Patient Blood Management Guidelines: Module 2

Perioperative

Technical Report

Volume 2b

Appendixes (question 3)

Introduction

This volume deals with question 3 of the systematic review for perioperative patient blood management.

In patients undergoing surgery, what is the effect of perioperative strategies that minimise blood loss on morbidity, mortality and blood transfusion?

This volume is accompanied by Volume 1b, which presents the systematic review of the evidence and the evidence-based recommendations for this question. Two other volumes – 1a and 2a – cover questions 1, 2 and 4–9. Dates covered by the literature searches are given in Chapter 2 of Volume 1a (see Table 2.1.1).

Question 3 includes the following 10 interventions:

- *Intervention 1* – acute normovolemic haemodilution (ANH)
- *Intervention 2* – intraoperative cell salvage
- *Intervention 3* – perioperative acute normovolemic haemodilution combined with intraoperative cell salvage
- *Intervention 4* – postoperative cell salvage
- *Intervention 5* – deliberate induced hypotension
- *Intervention 6* – prevention of hypothermia
- *Intervention 7* – point-of-care testing using thromboelastography
- *Intervention 8* – administration of antifibrinolytics (aprotinin, tranexamic acid, ε-aminocaproic acid) and desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP)
- *Intervention 9* – appropriate patient positioning
- *Intervention 10* – preoperative autologous donation (PAD).

Contents

Appendix A: Literature searches

EMBASE.com

Intervention 1 – Acute normovolemic haemodilution: Level I evidence

Search conducted 21 December 2009 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076417
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#3	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) NOT [30-7-2009]/sd	111681
#4	#1 AND #2 AND #3	20746
#5	'hemodilution' OR 'hemodilution'/exp OR hemodilution OR 'haemodilution' OR 'haemodilution'/exp OR haemodilution OR 'blood dilution'/exp OR 'blood dilution' NOT [30-7-2009]/sd	7601
#6	#21 AND #30	69

Intervention 1 – Acute normovolemic haemodilution: Level II evidence

Search conducted 3 January 2010 (January 2002 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd AND [2002-2010]/py	4357522
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471241
#3	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116315
#4	#1 AND #2 AND #3	123429
#5	'hemodilution'/exp OR hemodilution OR 'haemodilution'/exp OR haemodilution OR 'blood dilution'/exp OR 'blood dilution'	7739
#6	#8 AND #9	393

Interventions 2–4 – Intraoperative and postoperative cell salvage: Level I evidence

Search conducted 22 December 2009 (1966 to 30 July 2009)

Note: This search was used to locate Level I evidence for perioperative question 3, interventions 2– 4.

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076417
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#3	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) NOT [30-7-2009]/sd	111681
#4	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers' NOT [30-7-2009]/sd	12817
#5	#1 AND #2 AND #3 AND #4	129

Intervention 2 – Intraoperative cell salvage: Level II evidence

Search conducted 3 January 2010 (January 2004 to 30 July 2009)

#	Search	Results
#1	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471241
#2	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116315
#3	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076415
#4	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers' AND [2004-2010]/py	6710
#5	#1 AND #2 AND #3 AND #4	971

Intervention 3 – Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage: Level II evidence

Search conducted 3 January 2010 (1966 to 30 July 2009)

#	Search	Results
#1	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471241
#2	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116315
#3	'hemodilution'/exp OR hemodilution OR 'haemodilution'/exp OR haemodilution OR 'blood dilution'/exp OR 'blood dilution'	7739
#4	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076415
#5	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	13585
#6	#1 AND #2 AND #3 AND #4 AND #5	60

Intervention 3 – Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage: Level III and Level IV evidence

Search conducted 11 February 2010 (1966 to 30 July 2009)

#	Search	Results
#1	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' AND ('clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study') NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter) AND ('hemodilution'/exp OR hemodilution OR 'haemodilution'/exp OR haemodilution OR 'blood dilution'/exp OR 'blood dilution') AND ('surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period') NOT [30-7-2009]/sd AND ('blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers')	60
#2	'blood'/exp OR 'serum'/exp OR 'plasma'/exp OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anaemia'/exp	2459023
#3	'hemodilution'/exp OR 'haemodilution'/exp OR 'blood dilution'/exp	5588
#4	'surgery'/exp OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'postoperative period'/exp OR 'preoperative period'/exp NOT [30-7-2009]/sd	13076029
#5	'blood salvage'/exp OR 'salvage therapy'/exp OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	11918
#6	#2 AND #3 AND #4 AND #5	130
#7	#6 NOT #1	85

Intervention 4 – Postoperative cell salvage: Level II evidence

Search conducted 3 January 2010 (1966 to 30 July 2009)

#	Search	Results
#1	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471241
#2	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116315
#3	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076415
#4	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	13585
#5	postoperative OR 'post operative'	691807
#6	#1 AND #2 AND #3 AND #4 AND #5	292

Intervention 5 – Deliberate induced hypotension: Level I evidence

Search conducted 21 December 2009 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076417
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#3	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) NOT [30-7-2009]/sd	111681
#4	#1 AND #2 AND #3	20746
#5	'induced hypotension'/exp OR 'induced hypotension' OR 'controlled hypotension'/exp OR 'controlled hypotension' OR 'hypotensive anesthesia' OR 'hypotensive anaesthesia' OR 'hypotensive epidural anesthesia' OR 'hypotensive epidural anaesthesia' OR 'iatrogenic hypotension'/exp OR 'iatrogenic hypotension' NOT [30-6-2009]/sd	71749
#6	#4 AND #5	909

Intervention 5 – Deliberate induced hypotension: Level II evidence

Search conducted 5 January 2010 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period'	13433297
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471869
#3	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116696
#4	'induced hypotension'/exp OR 'induced hypotension' OR 'induced hypotension':ab,ti OR 'controlled hypotension':ab,ti OR 'iatrogenic hypotension':ab,ti OR 'hypotensive anaesthesia':ab,ti OR 'hypotensive anesthesia':ab,ti OR 'hypotensive epidural anesthesia':ab,ti OR 'hypotensive epidural anaesthesia':ab,ti NOT [30-7-2009]/sd	4580
#5	#1 AND #2 AND #3 AND #4	257

Intervention 6 – Prevention of hypothermia: Level I evidence

Search conducted 21 December 2009 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076417
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#3	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) NOT [30-7-2009]/sd	111681
#4	#1 AND #2 AND #3	20746
#5	'normothermia'/exp OR 'normothermia' OR 'thermoregulation'/exp OR 'thermoregulation' OR 'warming'/exp OR 'warming' OR 'hypothermia'/exp OR 'hypothermia' AND ('blood' OR 'blood'/exp OR blood OR hemorrhag* OR haemorrhag* OR 'anaemia' OR 'anaemia'/exp OR anaemia OR 'anemia' OR 'anemia'/exp OR anemia) NOT [30-7-2009]/sd	35595
#6	#4 and #5	158

Intervention 6 – Prevention of hypothermia: Level II evidence

Search conducted 5 January 2010 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period'	13433297
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471869
#3	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116696
#4	'hypothermia'/exp/dm_pc OR 'hypothermia' OR 'normothermia':ab,ti OR 'thermoregulation':ab,ti OR 'warming':ab,ti OR 'hypothermia':ab,ti OR ('hypothermia'/exp OR 'hypothermia' AND ('perioperative complication'/exp/dm_pc OR 'perioperative complication' OR 'peroperative complication'/exp/dm_pc OR 'peroperative complication' OR 'postoperative complication'/exp/dm_pc OR 'postoperative complication' OR 'prevention'/exp OR 'prevention' OR 'primary prevention'/exp OR 'primary prevention')) NOT [30-7-2009]/sd	44694
#5	#1 AND #2 AND #3 AND #4	1002

Intervention 7 – Point-of-care testing: Level I and Level II evidence

Search conducted 22 December 2009 for any type of point-of-care test (1966 to 30 July 2009)

#	Search	Results
#1	'comparative study'/exp OR 'randomised controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'parallel design'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR comparative OR 'open label' OR placebo OR randomi* OR 'double blind' OR 'single blind' OR controlled OR single OR (double AND dummy)	6119239
#2	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*))	118272
#3	#1 OR #2	6172408
#4	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#5	'point of care testing'/exp OR 'point of care testing' OR 'point of care' OR 'bedside' NEAR/3 'testing' OR 'bed side' NEAR/3 'testing' OR 'bedside' NEAR/3 'test' OR 'bed side' NEAR/3 'test' OR 'bedside' NEAR/3 'tests' OR 'bed side' NEAR/3 'tests' OR 'bedside' NEAR/3 'monitoring' OR 'bed side' NEAR/3 'monitoring' OR 'bedside' NEAR/3 'computing' OR 'bed side' NEAR/3 'computing' OR 'bedside' NEAR/3 'technology' OR 'bed side' NEAR/3 'technology' NOT [30-7-2009]/sd	5169
#6	#3 AND #4 AND #5	786

The preliminary literature search above found a limited body of comparative evidence for the effect of point-of-care testing other than thromboelastography (TEG) on mortality, morbidity and the need for allogeneic blood transfusion. A more focused literature search for specific tests was then conducted. The CRG subsequently made a decision to limit the scope of this intervention to comparative studies of TEG and TEG-based point-of-care tests.

Intervention 7 – Point-of-care testing: Level I-III evidence

Search conducted 2 February 2010 for specific point-of-care tests (1966 to 30 July 2009)

#	Search	Results
#1	'comparative study'/exp OR 'comparative study' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'parallel design'/exp OR 'parallel design' OR 'single blind procedure'/exp OR 'single blind procedure' OR comparative OR 'open label' OR 'placebo'/exp OR 'placebo' OR randomi* OR 'double blind' OR 'single blind' OR controlled OR single OR (double AND dummy) OR 'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) AND ('blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' AND bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia') AND ('point of care testing'/exp OR 'point of care testing' OR 'point of care' OR 'bedside' NEAR/3 'testing' OR 'bed side' NEAR/3 'testing' OR 'bedside' NEAR/3 'test' OR 'bed side' NEAR/3 'test' OR 'bedside' NEAR/3 'tests' OR 'bed side' NEAR/3 'tests' OR 'bedside' NEAR/3 'monitoring' OR 'bed side' NEAR/3 'monitoring' OR 'bedside' NEAR/3 'computing' OR 'bed side' NEAR/3 'computing' OR 'bedside' NEAR/3 'technology' OR 'bed side' NEAR/3 'technology') NOT [30-7-2009]/sd	786
#2	'blood'/exp OR 'serum'/exp OR 'plasma'/exp OR hemorrh* OR haemorrh* OR 'bleeding'/exp AND bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anaemia'/exp AND ('blood clotting parameters'/exp OR 'blood analysis'/exp OR 'blood examination'/exp)	100275
#3	'surgery'/exp OR 'surgery' OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076023
#4	'teg':ab,ti OR 'sonoclot':ab,ti OR 'rotem':ab,ti OR 'roteg':ab,ti OR hemocue OR 'international normalised ratio':ab,ti OR 'hemoglobin test':ab,ti OR 'hb test':ab,ti OR 'thromboelastograph':ab,ti OR 'thromboelastography':ab,ti OR 'thromboelastograpy':ab,ti OR 'hemoglobin blood level'/exp OR 'hemoglobin blood level' OR 'hemoglobin blood level':ab,ti OR 'thrombelastography':ab,ti OR 'haemoglobin blood level'/exp OR 'haemoglobin blood level'	11233
#5	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) OR 'comparative study'/exp OR 'comparative study' OR 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'parallel design'/exp OR 'parallel design' OR 'single blind procedure'/exp OR 'single blind procedure' OR comparative OR 'open label' OR 'placebo'/exp OR 'placebo' OR randomi* OR 'double blind' OR 'single blind' OR controlled OR single OR (double AND dummy)	6309867
#6	#1 OR (#2 AND #3 AND #4 AND #5)	1921

Intervention 8 – Administration of antifibrinolytics and DDAVP: Level I evidence

Search conducted 22 December 2009 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076417
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#3	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) NOT [30-7-2009]/sd	111681
#4	'antifibrinolytic agent'/exp OR 'antifibrinolytic agent' OR antifibrinolytic* OR 'anti fibrinolytic' OR 'anti fibrinolytics' OR antiplasmin* OR 'anti plasmin' OR 'anti plasmins' OR antifibrinolysin* OR 'anti fibrinolysin' OR 'anti fibrinolysins' OR 'fibrinolysis inhibitor'/exp OR 'fibrinolysis inhibitor' OR 'fibrinolysis inhibitors' OR 'plasmin inhibitor'/exp OR 'plasmin inhibitor' OR 'plamin inhibitors' OR 'tranexamic acid'/exp OR 'tranexamic acid' OR 'cyklokapron'/exp OR 'cyklokapron' OR 'aminocaproic acid'/exp OR 'aminocaproic acid' OR 'eaca'/exp OR 'eaca' OR 'amicar'/exp OR 'amicar' OR 'aprotinin'/exp OR 'aprotinin' OR 'trasylol'/exp OR 'trasylol' OR 'antilysin'/exp OR 'antilysin' OR 'desmopressin'/exp OR 'desmopressin' OR 'ddavp'/exp OR 'ddavp' OR '1197 18 8':rn OR '701 54 2':rn OR '1319 82 0':rn OR '60 32 2':rn OR '11004 21 0':rn OR '12407 79 3':rn OR '50936 63 5':rn OR '52229 70 6':rn OR '58591 29 0':rn OR '9050 74 2':rn OR '9075 10 9':rn OR '9087 70 1':rn OR '16679 58 6':rn OR '62288 83 9':rn OR '62357 86 2':rn NOT [30-7-2009]/sd	33573
#5	#1 AND #2 AND #3 AND #4	388

Intervention 8 – Administration of antifibrinolytics and DDAVP: Level II evidence for aprotinin

Search conducted 21 April 2010 (1 July 2006 to 30 July 2009)

#	Search	Results
#1	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1093468
#2	'surgery'/exp OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'postoperative period'/exp OR 'preoperative period'/exp NOT [30-7-2009]/sd	13076116
#3	'blood'/exp OR 'serum'/exp OR 'plasma'/exp OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anaemia'/exp	3541273
#4	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*))	104108
#5	'aprotinin'/exp OR 'aprotinin' OR 'trasylol'/exp OR 'trasylol' OR 'antilysin'/exp OR 'antilysin' OR '11004 21 0':rn OR '12407 79 3':rn OR '50936 63 5':rn OR '52229 70 6':rn OR '58591 29 0':rn OR '9050 74 2':rn OR '9075 10 9':rn OR '9087 70 1':rn AND [1-1-2006]/sd	1728
#6	#1 AND #2 AND #3 AND #5	371
#7	#2 AND #3 AND #4 AND #5	81
#8	#6 NOT #7	301

Intervention 8 – Administration of antifibrinolytics and DDAVP: Level II evidence for tranexamic acid and ε-aminocaproic acid

Search conducted 24 February 2010 (1 July 2006 to 30 July 2009)

#	Search	Results
#1	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1136181
#2	'surgery'/exp OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'postoperative period'/exp OR 'preoperative period'/exp NOT [30-7-2009]/sd	13076029
#3	'blood'/exp OR 'serum'/exp OR 'plasma'/exp OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anaemia'/exp	3491096
#4	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*))	121839
#5	'1319 82 0':rn OR '60 32 2':rn OR 'aminocaproic acid'/exp OR 'aminocaproic acid' OR 'eaca'/exp OR 'eaca' OR 'amicar'/exp OR 'amicar' OR '1197 18 8':rn OR '701 54 2':rn OR 'tranexamic acid'/exp OR 'tranexamic acid' OR 'cyklokapron'/exp OR 'cyklokapron' AND [1-7-2006]/sd	1600
#6	#1 AND #2 AND #3 AND #5	394
#7	#2 AND #3 AND #4 AND #5	88
#8	#6 NOT #7	321

Intervention 8 – Administration of antifibrinolytics and DDAVP: Level II evidence for DDAVP

Search conducted 16 February 2010 (January 2008 to 30 July 2009)

#	Search	Results
#1	'desmopressin'/exp OR 'desmopressin' OR 'ddavp'/exp OR 'ddavp' OR '16679 58 6':rn AND [2008-2010]/py	845
#2	'surgery'/exp OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'postoperative period'/exp OR 'preoperative period'/exp NOT [30-7-2009]/sd	13076029
#3	'blood'/exp OR 'serum'/exp OR 'plasma'/exp OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anaemia'/exp	3478770
#4	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1132142
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'pooled analysis' OR ('review'/exp AND ('meta analysis'/exp OR systemat* OR pool*))	100954
#6	#1 AND #2 AND #3 AND #4	84
#7	#1 AND #2 AND #3 AND #5	8
#8	#6 NOT #7	78

Intervention 9 – Appropriate patient positioning: Level I evidence

Search conducted 22 December 2009 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076417
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#3	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) NOT [30-7-2009]/sd	111681
#4	'patient positioning'/exp OR 'patient positioning' OR 'position'/exp OR 'position' OR 'semi sitting' OR 'operative positioning' OR 'lateral position' OR (patient* AND position*) NOT [30-7-2009]/sd	323990
#5	#1 AND #2 AND #3 AND #4	468

Intervention 9 – Appropriate patient positioning: Level II evidence

Search conducted 3 January 2010 (1966 to 30 July 2009)

#	Search	Results
#1	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471241
#2	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116315
#3	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076415
#4	'patient positioning'/exp OR 'patient positioning' OR 'position'/exp OR 'position' OR 'semi sitting' OR 'operative positioning' OR 'lateral position' OR (patient* AND position*) AND ('blood' OR 'blood'/exp OR blood OR hemorrhag* OR haemorrhag* OR 'anaemia' OR 'anaemia'/exp OR anaemia OR 'anemia' OR 'anemia'/exp OR anemia)	56266
#5	#1 AND #2 AND #3 AND #4	1640

Intervention 10 – Preoperative autologous donation: Level I evidence

Search conducted 22 December 2009 (1966 to 30 July 2009)

#	Search	Results
#1	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076417
#2	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia' NOT [30-7-2009]/sd	2398903
#3	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND ('meta analysis'/exp OR 'meta analysis' OR systemat* OR pool*)) NOT [30-7-2009]/sd	111681
#4	#1 AND #2 AND #3	20746
#5	'autohemotransfusion' OR 'autohemotransfusion'/exp OR autohemotransfusion OR autohaemotransfusion OR 'autotransfusion' OR 'autotransfusion'/exp OR autotransfusion OR autotransfus* OR ('blood' OR 'blood'/exp OR blood OR 'plasma' OR 'plasma'/exp OR plasma AND (autologous* OR predonat* OR donat* OR predeposit* OR deposit*)) NOT [30-7-2009]/sd	101841
#6	#4 AND #5	479

Intervention 10 – Preoperative autologous donation: Level II evidence

Search conducted 3 January 2010 (January 2004 to 30 July 2009)

#	Search	Results
#1	'blood'/exp OR 'blood' OR 'serum'/exp OR 'serum' OR 'plasma'/exp OR 'plasma' OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR 'bleeding' OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anemia' OR 'anaemia'/exp OR 'anaemia'	2471241
#2	'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR randomization OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo OR randomi?ed:ab,ti OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR (allocated NEAR/2 random*):ab,ti OR 'single blind':ab,ti OR 'single blinded':ab,ti OR 'double blind':ab,ti OR 'double blinded':ab,ti OR 'treble blind':ab,ti OR 'treble blinded':ab,ti OR 'triple blind':ab,ti OR 'triple blinded':ab,ti OR placebo*:ab,ti OR 'prospective study'/exp OR 'prospective study' NOT ('case study'/exp OR 'case study' OR 'case report':ab,ti OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR letter)	1116315
#3	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period' NOT [30-7-2009]/sd	13076415
#4	'autohemotransfusion' OR 'autohemotransfusion'/exp OR autohemotransfusion OR 'autotransfusion' OR 'autotransfusion'/exp OR autotransfusion OR autotransfus* OR (autologous* AND transfus*) AND [2004-2010]/py	4413
#5	#1 AND #2 AND #3 AND #4	927

Perioperative Question 3 – Quality of life: not limited by study type

Search conducted 14 February 2010 (1966 to 30 July 2009)

Note: Higher levels of evidence did not capture quality of life as an outcome for any of the interventions in perioperative question 3. This literature search was intended to identify clinical studies of any type that are relevant to perioperative question 3 and report quality of life as a key outcome.

#	Search	Results
#1	'quality of life'/exp	144031
#2	'surgery'/exp OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'postoperative period'/exp OR 'preoperative period'/exp NOT [30-7-2009]/sd	13076029
#3	'blood'/exp OR 'serum'/exp OR 'plasma'/exp OR hemorrh* OR haemorrh* OR 'bleeding'/exp OR bleed* OR hemarthros* OR haemarthros* OR hemat* OR haemat* OR hemoperi* OR haemoperi* OR 'anemia'/exp OR 'anaemia'/exp	3475166
#4	#1 AND #2 AND #3	17977
#5	'hemodilution'/exp OR 'haemodilution'/exp OR 'blood dilution'/exp	5588
#6	'blood salvage'/exp OR 'salvage therapy'/exp OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	11923
#7	'induced hypotension'/exp OR 'controlled hypotension'/exp OR 'hypotensive anesthesia' OR 'hypotensive anaesthesia' OR 'hypotensive epidural anesthesia' OR 'hypotensive epidural anaesthesia' OR 'iatrogenic hypotension'/exp	74657
#8	'normothermia'/exp OR 'thermoregulation'/exp OR 'warming'/exp OR 'hypothermia'/exp	84849
#9	'antifibrinolytic agent'/exp OR antifibrinolytic* OR 'anti fibrinolytic' OR 'anti fibrinolytics' OR antiplasmin* OR 'anti plasmin' OR 'anti plasmins' OR antifibrinolysin* OR 'anti fibrinolysin' OR 'anti fibrinolysins' OR 'fibrinolysis inhibitor'/exp OR 'fibrinolysis inhibitors' OR 'plasmin inhibitor'/exp OR 'plamin inhibitors' OR 'tranexamic acid'/exp OR 'cyklokapron'/exp OR 'aminocaproic acid'/exp OR 'eaca'/exp OR 'amicar'/exp OR 'aprotinin'/exp OR 'trasylol'/exp OR 'antilysin'/exp OR 'desmopressin'/exp OR 'ddavp'/exp OR '1197 18 8':rn OR '701 54 2':rn OR '1319 82 0':rn OR '60 32 2':rn OR '11004 21 0':rn OR '12407 79 3':rn OR '50936 63 5':rn OR '52229 70 6':rn OR '58591 29 0':rn OR '9050 74 2':rn OR '9075 10 9':rn OR '9087 70 1':rn OR '16679 58 6':rn OR '62288 83 9':rn OR '62357 86 2'	30091
#10	'patient positioning'/exp OR 'position'/exp OR 'semi sitting' OR 'operative positioning' OR 'lateral position' OR (patient* AND position*)	156770
#11	'autohemotransfusion'/exp OR autohaemotransfusion OR 'autotransfusion'/exp OR autotransfus* OR ('blood'/exp OR 'plasma'/exp AND (autologous* OR predonat* OR donat* OR predeposit* OR deposit*))	39281
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	393199
#13	#4 AND #12	1173

Cochrane Library

Intervention 1 – Acute normovolemic haemodilution: Level I evidence

Search conducted 21 December 2009

ID	Search	Results
#1	MeSH descriptor Hemodilution, this term only	341
#2	(acute AND (normovolemic OR normovolaemic))	157
#3	(acute AND ("normo volemic" OR "normo volaemic"))	0
#4	(acute NEAR/2 ("normovolemic hemodilution" OR "normovolemic haemodilution"))	102
#5	(acute NEAR/2 ("normovolaemic hemodilution" OR "normovolaemic haemodilution"))	50
#6	(acute NEAR/2 ("normo volemic hemodilution" OR "normo volemic haemodilution"))	0
#7	(acute NEAR/2 ("normo volaemic hemodilution" OR "normo volaemic haemodilution"))	0
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	408

Citations identified in 'Cochrane reviews', 'Database of systematic reviews' and 'Technological assessments' were exported into reference manager. Total number of citations exported: 25

Intervention 1 – Acute normovolemic haemodilution: Level II evidence

Search conducted 3 January 2010

ID	Search	Results
#1	MeSH descriptor Hemodilution, this term only	346
#2	acute AND (normovolemic OR normovolaemic OR 'normo volemic' OR 'normo volaemic')	158
#3	(acute NEAR/2 ("normovolemic hemodilution" OR "normovolemic haemodilution"))	103
#4	(acute NEAR/2 ("normovolaemic hemodilution" OR "normovolaemic haemodilution"))	51
#5	(acute NEAR/2 ("normo volemic hemodilution" OR "normo volemic haemodilution"))	0
#6	(acute NEAR/2 ("normo volaemic hemodilution" OR "normo volaemic haemodilution"))	0
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6), from 2002 to 2010	141

Citations identified in 'Central register of clinical trials' exported into reference manager. Number of citations exported: 116

Interventions 2–4 – Intraoperative and postoperative cell salvage: Level I evidence

Search conducted 22 December 2009

Note: This search was used to locate Level I evidence for Perioperative question 3 interventions 2 to 4.

ID	Search	Results
#1	MeSH descriptor Salvage Therapy explode all trees	365
#2	"blood salvage" OR "salvage therapy" OR "cell salvage" OR "erythrocyte salvage" OR "cell saver" OR "Cell savers"	742
#3	#1 OR #2	742

Citations identified in 'Cochrane Reviews', 'Database of systematic reviews' and 'Technological assessments' were exported into reference manager. Total number of citations exported: 72

Interventions 2–4 – Intraoperative and postoperative cell salvage: Level II evidence

Search conducted 3 January 2010

ID	Search	Results
#1	MeSH descriptor Salvage Therapy explode all trees	365
#2	"blood salvage" OR "salvage therapy" OR "cell salvage" OR "erythrocyte salvage" OR "cell saver" OR "Cell savers"	742
#3	(#1 OR #2), from 2004 to 2010	314

Citations identified in 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 228

Intervention 3 – Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage: Level II evidence

Search conducted 3 January 2010

ID	Search	Results
#1	MeSH descriptor Salvage Therapy explode all trees	365
#2	"blood salvage" OR "salvage therapy" OR "cell salvage" OR "erythrocyte salvage" OR "cell saver" OR "Cell savers"	742
#3	#1 OR #2	742
#4	MeSH descriptor Hemodilution, this term only	341
#5	(acute AND (normovolemic OR normovolaemic))	157
#6	(acute AND ("normo volemic" OR "normo volaemic"))	0
#7	(acute NEAR/2 ("normovolemic hemodilution" OR "normovolemic haemodilution"))	102
#8	(acute NEAR/2 ("normovolaemic hemodilution" OR "normovolaemic haemodilution"))	50
#9	(acute NEAR/2 ("normo volemic hemodilution" OR "normo volemic haemodilution"))	0
#10	(acute NEAR/2 ("normo volaemic hemodilution" OR "normo volaemic haemodilution"))	0
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	408
#12	#3 AND #11	31

Citations identified in 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 17

Intervention 5 – Deliberate induced hypotension: Level I and Level II evidence

Search conducted 21 December 2009

ID	Search	Results
#1	MeSH descriptor Hypotension explode all trees with qualifier: PC	258
#2	"induced hypotension"	305
#3	"controlled hypotension" OR "iatrogenic hypotension"	119
#4	(#1 OR #2 OR #3)	614

Citations identified in 'Cochrane reviews', 'Database of systematic reviews', and 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 613

Intervention 6 – Prevention of hypothermia: Level I and Level II evidence

Search conducted 22 December 2009

#	Search	Results
#1	MeSH descriptor Hypothermia explode all trees with qualifier: PC	141
#2	(hypothermia AND prevent*):ti	57
#3	(prevent* NEAR/20 hypothermia)	347
#4	(#1 OR #2 OR #3)	347

Citations identified in 'Cochrane reviews', 'Database of systematic reviews', and 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 342

Intervention 7 – Point-of-care testing: Level I and Level II evidence

Search conducted 22 December 2009 for any point-of-care tests

ID	Search	Results
#1	MeSH descriptor Point-of-Care Systems, this term only	234
#2	"point of care"	343
#3	(bedside OR "bed side") NEAR/3 (test OR tests OR testing)	51
#4	(bedside OR "bed side") NEAR/3 monitoring	36
#5	(bedside OR "bed side") NEAR/3 computing	0
#6	(bedside OR "bed side") NEAR/3 technology	9
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	405

Citations identified in 'Cochrane Reviews', 'Database of systematic reviews', 'Central register of clinical trials', and 'Technological assessments' were exported into reference manager. Total number of citations exported: 64

Intervention 7 – Point-of-care testing using thromboelastography: Level I and Level II evidence

Search conducted 2 February 2010 for specific point-of-care tests

ID	Search	Results
#1	MeSH descriptor Thrombelastography explode all trees	114
#2	Sonoclot	8
#3	rotem	20
#4	roteg	5
#5	"international normalized ratio"	536
#6	"international normalised ratio"	137
#7	"haemoglobin test"	2
#8	"hemoglobin test"	4
#9	surgery	84598
#10	transplant*	17598
#11	reconstruct*	3403
#12	operat*	33199
#13	preoperat*	13310
#14	intraoperat*	8780
#15	perioperat*	5575
#16	peroperat*	506
#17	postoperat*	43291
#18	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	119171
#19	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	780
#20	(#18 AND #19)	265

Citations identified in 'Cochrane Reviews', 'Database of systematic reviews', 'Central register of clinical trials', and 'Technological Assessments' were exported into reference manager. Total number of citations exported: 243

Intervention 8 – Administration of antifibrinolytics & DDAVP: Level I evidence

Search conducted 22 December 2009

ID	Search	Results
#1	MeSH descriptor Antifibrinolytic Agents, this term only	299
#2	MeSH descriptor Tranexamic Acid, this term only	253
#3	MeSH descriptor Aprotinin, this term only	497
#4	MeSH descriptor Deamino Arginine Vasopressin, this term only	274
#5	(antifibrinolytic* OR "anti fibrinolytic" OR "anti fibrinolytics")	495
#6	(antiplasmin* OR "anti plasmin" OR "anti plasmins")	260
#7	(antifibrinolysin* OR "anti fibrinolysin" OR "anti fibrinolysins")	3
#8	"fibrinolysis inhibitor" OR "fibrinolysis inhibitors"	33
#9	"plasmin inhibitor" OR "plamin inhibitors"	54
#10	"tranexamic acid" OR Cyklokapron	450
#11	"aminocaproic acid" OR eaca OR Amicar	172
#12	(aprotinin OR Trasylol OR antilysin)	783
#13	(desmopressin OR ddavp)	454
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	2072

Citations identified in 'Cochrane Reviews', 'Database of systematic reviews' and 'Technological assessments' were exported into reference manager. Total number of citations exported: 106

Intervention 8 – Administration of antifibrinolytics & DDAVP: Level II evidence for aprotinin

Search conducted 22 April 2010

ID	Search	Results
#1	aprotinin OR trasylol OR antilysin, from 2006 to 2009	78

Citations identified in 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 49

Intervention 8 – Administration of antifibrinolytics & DDAVP: Level II evidence for tranexamic acid and ε-aminocaproic acid

Search conducted 17 February 2010

ID	Search	Results
#1	"tranexamic acid" OR Cyklokapron OR "aminocaproic acid" OR eaca OR Amicar, from 2006 to 2009	125

Citations identified in 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 82

Intervention 8 – Administration of antifibrinolytics & DDAVP: Level II evidence for DDAVP

Search conducted 17 February 2010

ID	Search	Results
#1	MeSH descriptor Deamino Arginine Vasopressin, this term only	275
#2	desmopressin OR ddavp	457
#3	(#1 OR #2), from 2008 to 2010	39

Citations identified in 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 17

Intervention 9 – Appropriate patient positioning: Level I evidence

Search conducted 22 December 2009

ID	Search	Results
#1	MeSH descriptor Posture explode all trees	2746
#2	(patient OR patients) AND position*:ti	732
#3	(patient OR patients) NEAR/20 position*	2585
#4	(#35 OR #36 OR #37)	4856

Citations identified in 'Cochrane Reviews', 'Database of systematic reviews' and 'Technological assessments' were exported into reference manager. Total number of citations exported: 257

Intervention 9 – Appropriate patient positioning: Level II evidence

Search conducted 3 January 2010

ID	Search	Results
#1	MeSH descriptor Posture explode all trees	2746
#2	(patient OR patients) AND position*:ti	732
#3	(patient OR patients) NEAR/20 position*	2585
#4	(#1 OR #2 OR #3)	4856
#5	blood OR serum OR plasma OR hemorrh* OR haemorrh* OR bleed* OR hemarthros* OR haemorthros* OR hemat* OR haemat* or hemoperi* OR haemoperi* OR anemia	190593
#6	(#4 AND #5)	1807
#7	posture	3447
#8	(minimis* NEAR/5 ("blood loss" OR transfusion*))	28
#9	(minimiz* NEAR/5 ("blood loss" OR transfusion*))	53
#10	(reduc* NEAR/5 ("blood loss" OR transfusion*))	1529
#11	(minimis* AND ("blood loss" OR transfusion*)):ti	12
#12	(minimiz* AND ("blood loss" OR transfusion*)):ti	14
#13	(reduc* AND ("blood loss" OR transfusion*)):ti	391
#14	(#8 OR #9 OR #10 OR #11 OR #12 OR #13)	1595
#15	(#4 AND #14)	10

Citations identified in 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 6

Intervention 10 – Preoperative autologous donation: Level I and Level II evidence

Search conducted 22 December 2009

ID	Search	Results
#1	MeSH descriptor Blood Transfusion, Autologous explode all trees	586
#2	autologous	3986
#3	MeSH descriptor Blood Donors, this term only	267
#4	donor* OR donation* OR deposit* OR collection	17709
#5	#3 OR #4	17709
#6	#5 AND #2	787
#7	autologous NEAR/1 donor*	16
#8	(autologous NEAR/1 (predeposit* OR "pre deposit" OR "pre deposits"))	17
#9	(Autologous NEAR/1 Predonation*)	10
#10	("predeposit autologous" OR "pre deposit autologous") NEAR/1 donation	0
#11	"predonated autologous blood" OR "pre donated autologous blood"	11
#12	(predonation OR "pre donation") NEAR/1 "autologous blood"	1
#13	("preoperative autologous" OR "pre operative autologous") NEAR/1 deposit*	0
#14	("preoperative autologous" OR "pre operative autologous") NEAR/1 donation	1
#15	("preoperative donation" OR "pre operative donation") NEAR/1 "autologous blood"	0
#16	"preoperatively donated autologous blood" OR "pre operatively donated autologous blood"	4
#17	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16), from 2004 to 2010	260

Citations identified in 'Cochrane Reviews', 'Database of systematic reviews', 'Technological Assessments', and 'Central register of clinical trials' were exported into reference manager. Total number of citations exported: 293

CINAHL (Nursing and Allied Health)

Search conducted 19 June 2009 (1982 to present)

ID	Query	Results
S114	S32 or S43 or S51 or S56 or S60 or S68 or S82 or S87 or S113	293
S113	S17 and S112	51
S112	S96 or S97 or S98 or S99 or S100 or S101 or S102 or S103 or S104 or S105 or S106 or S107 or S108 or S109 or S110 or S111	95
S111	TI ("preoperatively donated autologous blood" OR "pre operatively donated autologous blood") or AB ("preoperatively donated autologous blood" OR "pre operatively donated autologous blood")	1
S110	TI "pre operative donation" N1 "autologous blood" or AB "pre operative donation" N1 "autologous blood"	0
S109	TI "preoperative donation" N1 "autologous blood" or AB "preoperative donation" N1 "autologous blood"	2
S108	TI "pre operative autologous" N1 donation or AB "pre operative autologous" N1 donation	1
S107	TI "preoperative autologous" N1 donation or AB "preoperative autologous" N1 donation	32
S106	TI "pre operative autologous" N1 deposit* or AB "pre operative autologous" N1 deposit*	0
S105	TI "preoperative autologous" N1 deposit* or AB "preoperative autologous" N1 deposit*	1
S104	TI "pre donation" N1 "autologous blood" or AB "pre donation" N1 "autologous blood"	1
S103	TI predonation N1 "autologous blood" or AB predonation N1 "autologous blood"	0
S102	TI ("predonated autologous blood" OR "pre donated autologous blood") or AB ("predonated autologous blood" OR "pre donated autologous blood")	0
S101	TI "pre deposit autologous" N1 donation or AB "pre deposit autologous" N1 donation	1
S100	TI "predeposit autologous" N1 donation or AB "predeposit autologous" N1 donation	0
S99	TI Autologous N1 Predonation* or AB Autologous N1 Predonation*	5
S98	TI (autologous N1 (predeposit* OR "pre deposit" OR "pre deposits")) or AB (autologous N1 (predeposit* OR "pre deposit" OR "pre deposits"))	4
S97	TI autologous N1 donor* or AB autologous N1 donor*	18
S96	S90 and S93 and S95	73
S95	S7 or S9 or S94	12748
S94	(MH "Preoperative Care+")	6957
S93	S91 or S92	24193
S92	TI (donor* OR donation* OR deposit* OR collection) or AB (donor* OR donation* OR deposit* OR collection)	23720
S91	(MH "Blood Donors")	1344
S90	S88 or S89	1992
S89	TI autologous or AB autologous	1723
S88	(MH "Blood Transfusion, Autologous")	470
S87	S18 and S86	11
S86	S83 or S84 or S85	11301
S85	TI (patients AND position*) or AB (patients AND position*)	5798
S84	TI (patient AND position*) or AB (patient AND position*)	3424
S83	(MH "Patient Positioning+")	4774
S82	S18 and S81	100
S81	S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80	722
S80	TI (desmopressin OR ddavp) or AB (desmopressin OR ddavp)	128

S79	TI (aprotinin OR Trasylol OR antilysin) or AB (aprotinin OR Trasylol OR antilysin)	202
S78	TI ("aminocaproic acid" OR eaca OR Amicar) or AB ("aminocaproic acid" OR eaca OR Amicar)	54
S77	TI ("tranexamic acid" OR Cyklokapron) or AB ("tranexamic acid" OR Cyklokapron)	82
S76	TI ("plasmin inhibitor" OR "plamin inhibitors") or AB ("plasmin inhibitor" OR "plamin inhibitors")	9
S75	TI ("fibrinolysis inhibitor" OR "fibrinolysis inhibitors") or AB ("fibrinolysis inhibitor" OR "fibrinolysis inhibitors")	21
S74	TI (antifibrinolysin* OR "anti fibrinolysin" OR "anti fibrinolysins") or AB (antifibrinolysin* OR "anti fibrinolysin" OR "anti fibrinolysins")	0
S73	TI (antiplasmin* OR "anti plasmin" OR "anti plasmins") or AB (antiplasmin* OR "anti plasmin" OR "anti plasmins")	41
S72	TI (antifibrinolytic* OR "anti fibrinolytic" OR "anti fibrinolytics") or AB (antifibrinolytic* OR "anti fibrinolytic" OR "anti fibrinolytics")	76
S71	(MH "Desmopressin")	177
S70	(MH "Aprotinin")	207
S69	(MH "Antifibrinolytic Agents")	167
S68	S18 and S67	55
S67	S61 or S62 or S63 or S64 or S65 or S66	76034
S66	TI ("bed side" N3 (monitoring OR computing OR technology)) or AB ("bed side" N3 (monitoring OR computing OR technology))	22000
S65	TI (bedside N3 (monitoring OR computing OR technology)) or AB (bedside N3 (monitoring OR computing OR technology))	22108
S64	TI ("bed side" N3 (test OR tests OR testing)) or AB ("bed side" N3 (test OR tests OR testing))	53967
S63	TI (bedside N3 (test OR tests OR testing)) or AB (bedside N3 (test OR tests OR testing))	54015
S62	TI "point of care" or AB "point of care"	1030
S61	(MH "Point-of-Care Testing")	909
S60	S18 and S59	10
S59	S57 or S58	516
S58	TI (hypothermia AND prevent*) or AB (hypothermia AND prevent*)	215
S57	(MH "Hypothermia/PC")	382
S56	S18 and S55	10
S55	S52 or S53 or S54	256
S54	TI ("controlled hypotension" OR "iatrogenic hypotension") or AB ("controlled hypotension" OR "iatrogenic hypotension")	13
S53	TI "induced hypotension" or AB "induced hypotension"	55
S52	(MH "Hypotension+/CI")	203
S51	S17 and S50	73
S50	S46 or S47 or S48 or S49	200
S49	TI ("postoperative blood salvage" OR "post operative blood salvage") or AB ("postoperative blood salvage" OR "post operative blood salvage")	14
S48	TI "post operative" N2 "cell salvage" or AB "post operative" N2 "cell salvage"	1
S47	TI postoperative N2 "cell salvage" or AB postoperative N2 "cell salvage"	3
S46	S35 and S45	199
S45	S3 or S4 or S12 or S44	35418
S44	(MH "Postoperative Care+")	7051
S43	S17 and S42	87

S42	S38 or S39 or S40 or S41	167
S41	TI ("intraoperative blood salvage" OR "intra operative blood salvage") or AB ("intraoperative blood salvage" OR "intra operative blood salvage")	10
S40	TI "intra operative" N2 "cell salvage" or AB "intra operative" N2 "cell salvage"	2
S39	TI intraoperative N2 "cell salvage" or AB intraoperative N2 "cell salvage"	6
S38	S35 and S37	164
S37	S5 or S6 or S10 or S36	6697
S36	(MH "Intraoperative Care+")	2766
S35	S33 or S34	1006
S34	(MH "Salvage Therapy")	461
S33	(MH "Blood Salvage+")	546
S32	S18 and S31	13
S31	S23 or S24	31
S30	TI acute N2 "normo volaemic haemodilution" or AB acute N2 "normo volaemic haemodilution"	0
S29	TI acute N2 "normo volaemic hemodilution" or AB acute N2 "normo volaemic hemodilution"	0
S28	TI (acute N2 ("normo volaemic hemodilution" OR "normo volaemic haemodilution") or AB (acute N2 ("normo volaemic hemodilution" OR "normo volaemic haemodilution")	0
S27	TI acute N2 "normo volemic haemodilution" or AB acute N2 "normo volemic haemodilution"	0
S26	TI acute N2 "normovolaemic hemodilution" or AB acute N2 "normovolaemic hemodilution"	0
S25	TI (acute N2 ("normovolaemic hemodilution" OR "normovolaemic haemodilution") or AB (acute N2 ("normovolaemic hemodilution" OR "normovolaemic haemodilution")	0
S24	TI (acute N2 ("normovolemic hemodilution" OR "normovolemic haemodilution")) or AB (acute N2 ("normovolemic hemodilution" OR "normovolemic haemodilution"))	27
S23	S19 and S22	27
S22	S20 or S21	36
S21	TI (acute AND ("normo volemic" OR "normo volaemic")) or AB (acute AND ("normo volemic" OR "normo volaemic"))	0
S20	TI (acute AND (normovolemic OR normovolaemic)) or AB (acute AND (normovolemic OR normovolaemic))	36
S19	(MH "Hemodilution")	158
S18	S13 and S17	839
S17	S14 or S15 or S16	4531
S16	TI (reduc* n5 ("blood loss" OR transfusion*)) or AB (reduc* N5 ("blood loss" OR transfusion*))	4510
S15	TI (minimiz* N5 ("blood loss" OR transfusion*)) or AB (minimiz* N5 ("blood loss" OR transfusion*))	4409
S14	TI (minimis* N5 ("blood loss" OR transfusion*)) or AB (minimis* N5 ("blood loss" OR transfusion*))	4384
S13	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12	54847
S12	TI (postoperative OR "post operative") or AB (postoperative OR "post operative")	14541
S11	TI (peroperative OR "per operative") or AB (peroperative OR "per operative")	51
S10	TI (intraoperative OR "intra operative") or AB (intraoperative OR "intra operative")	2995
S9	TI (preoperative OR "pre operative") or AB (preoperative OR "pre operative")	7264
S8	TI (perioperative OR "peri operative") or AB (perioperative OR "peri operative")	5356
S7	MH "Preoperative Period+"	725
S6	MH "Intraoperative Period"	367
S5	MH "Intraoperative Complications+"	1821

S4	MH "Postoperative Period"	1923
S3	MH "Postoperative Complications+"	21486
S2	MH "Perioperative Nursing"	8857
S1	MH "Perioperative Care+"	16222

AMI

Search conducted 19 June 2009 (1968 to present)

ID	Search Terms	Results
#7	((TI=(reduc* AND ("blood loss" OR transfusion*))) OR (TI=(minimiz* AND ("blood loss" OR transfusion*))) OR (TI=(minimis* AND ("blood loss" OR transfusion*))) OR (TI=(reduc* %5 ("blood loss" OR transfusion*)) OR AB=(reduc* %5 ("blood loss" OR transfusion*))) OR (TI=(minimiz* %5 ("blood loss" OR transfusion*)) OR AB=(minimiz* %5 ("blood loss" OR transfusion*))) OR (TI=(minimis* %5 ("blood loss" OR transfusion*)) OR AB=(minimis* %5 ("blood loss" OR transfusion*))))	48
#6	TI=(reduc* AND ("blood loss" OR transfusion*))	7
#5	TI=(minimiz* AND ("blood loss" OR transfusion*))	0
#4	TI=(minimis* AND ("blood loss" OR transfusion*))	1
#3	TI=(reduc* %5 ("blood loss" OR transfusion*)) OR AB=(reduc* %5 ("blood loss" OR transfusion*))	43
#2	TI=(minimiz* %5 ("blood loss" OR transfusion*)) OR AB=(minimiz* %5 ("blood loss" OR transfusion*))	0
#1	TI=(minimis* %5 ("blood loss" OR transfusion*)) OR AB=(minimis* %5 ("blood loss" OR transfusion*))	4

Appendix B: Excluded studies

This appendix documents studies that met inclusion criteria determined by PICO criteria, but were later excluded. These studies, and their reasons for exclusion, are listed below.

Intervention 8 – Administration of antifibrinolytics and DDAVP

Only three studies that met inclusion criteria were subsequently excluded from the evaluation; these are noted in the technical report and shown below. The reason for exclusion was the lack of pooling of data in the systematic review. Due to the large number of identified systematic reviews which included pooled data (30 systematic reviews), it was decided that these additional studies would not add substantial additional data to the evaluation.

Erstad BL. Systemic hemostatic medications for reducing surgical blood loss. *Ann Pharmacother* 35:925–934, 2001.

Fergusson D, VanWalraven C, Coyle D, Laupacis A. Economic evaluations of technologies to minimize perioperative transfusion: A systematic review of published studies. *Transfus Med Rev* 13:106–117, 1999.

Thiagarajamurthy S, Levine A, Dunning J. Does prophylactic tranexamic acid safely reduce bleeding without increasing thrombotic complications in patients undergoing cardiac surgery? *Interact Cardiovasc Thorac Surg* 3:489-494, 2004.

Appendix C: Literature search results

Intervention 1 – Acute normovolemic haemodilution

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*69*
Initial number of citations (Cochrane Library)	*25*
Number of duplicates	*5*
Number of citations searched by title/abstract	*89*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	34
Wrong intervention	45
Wrong comparator	0
Wrong indication	0
Wrong outcome	1
Number of citations retrieved	*9*
Citations retrieved from manual search	*1*
Full paper	
Not a clinical study	3
Wrong intervention	2
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Number of citations included	*5*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*393*
Initial number of citations (Cochrane Library)	*116*
Number of duplicates	*25*
Number of citations searched by title/abstract	*484*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	205
Wrong intervention	234
Wrong comparator	3
Wrong indication	3
Wrong outcome	13
Not an RCT	4
Not in English	8
Number of citations retrieved	*14*
Citations retrieved from manual search	*2*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Full paper	
Not a clinical study	0
Wrong intervention	2
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Number of citations included	*14*

Intervention 2 – Intraoperative cell salvage

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*129*
Initial number of citations (Cochrane Library)	*72*
Number of duplicates	*41*
Number of citations searched by title/abstract	*160*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	27
Wrong intervention	115
Wrong comparator	0
Wrong indication	8
Wrong outcome	0
Number of citations retrieved	*10*
Citations retrieved from manual search	*1*
Full paper	
Not a clinical study	3
Wrong intervention	2
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Not a SR	1
Number of citations included	*5*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*971*
Initial number of citations (Cochrane Library)	*228*
Number of duplicates	*84*
Number of citations searched by title/abstract	*1115*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	329
Wrong intervention	741
Wrong comparator	0
Wrong indication	0
Wrong outcome	2
Not an RCT	14
Number of citations retrieved	*29*
Citations retrieved from manual search	*4*
Full paper	
Not a clinical study	1
Wrong intervention	18
Wrong comparator	1
Wrong indication	0

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Wrong outcome	1
Not in English	1
Not an RCT	2
Number of citations included	*9*

Intervention 3 – Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*129*
Initial number of citations (Cochrane Library)	*72*
Number of duplicates	*41*
Number of citations searched by title/abstract	*160*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	27
Wrong intervention	115
Wrong comparator	0
Wrong indication	8
Wrong outcome	0
Number of citations retrieved	*10*
Citations retrieved from manual search	*1*
Full paper	
Not a clinical study	3
Wrong intervention	7
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Not a SR	1
Number of citations included	*0*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*60*
Initial number of citations (Cochrane Library)	*228*
Number of duplicates	*14*
Number of citations searched by title/abstract	*274*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	45
Wrong intervention	216
Wrong comparator	2
Wrong indication	4
Wrong outcome	0
Not an RCT	3
Not in English	1
Number of citations retrieved	*3*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	0
Wrong intervention	0

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Not in English	0
Not an RCT	0
Number of citations included	*3*

LEVEL III AND IV EVIDENCE	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*85*
Initial number of citations (Cochrane Library)	*0*
Number of duplicates	*2*
Number of citations searched by title/abstract	*83*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	49
Wrong intervention	30
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Not an RCT	0
Not in English	2
Individual case study	2
Number of citations retrieved	*0*
Citations retrieved from manual search	*0*

Intervention 4 – Postoperative cell salvage

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*129*
Initial number of citations (Cochrane Library)	*72*
Number of duplicates	*41*
Number of citations searched by title/abstract	*160*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	27
Wrong intervention	115
Wrong comparator	0
Wrong indication	8
Wrong outcome	0
Number of citations retrieved	*10*
Citations retrieved from manual search	*1*
Full paper	
Not a clinical study	3
Wrong intervention	2
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Not a SR	1
Number of citations included	*5*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*292*
Initial number of citations (Cochrane Library)	*17*
Number of duplicates	*9*
Number of citations searched by title/abstract	*300*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	70
Wrong intervention	213
Wrong comparator	1
Wrong indication	0
Wrong outcome	1
Not in English	1
Not an RCT	12
Number of citations retrieved	*2*
Citations retrieved from manual search	*1*
Full paper	
Not a clinical study	0
Wrong intervention	0
Wrong comparator	0

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Wrong indication	0
Wrong outcome	0
Not in English	0
Not an RCT	0
Number of citations included	*3*

Intervention 5 – Deliberate induced hypotension

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*909*
Initial number of citations (Cochrane Library)	*16*
Number of duplicates	*6*
Number of citations searched by title/abstract	*919*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	12
Wrong intervention	895
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Number of citations retrieved	*12*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	7
Wrong intervention	1
Wrong comparator	0
Wrong outcome	1
Not in English	1
Insufficient data	1
Number of citations included	*1*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*257*
Initial number of citations (Cochrane Library)	*597*
Number of duplicates	*107*
Number of citations searched by title/abstract	*747*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	58
Wrong intervention	524
Wrong comparator	33
Wrong indication	0
Wrong outcome	17
Not in English	77
Citations included in Level I evidence	*11*
Number of citations retrieved	*27*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	2
Wrong intervention	2
Wrong comparator	7

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Wrong outcome	1
Not in English	4
Publication not available	1
Number of citations included	*10*

Intervention 6 – Prevention of hypothermia

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*158*
Initial number of citations (Cochrane Library)	*23*
Number of duplicates	*1*
Number of citations searched by title/abstract	*180*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	1
Wrong intervention	0
Wrong comparator	0
Wrong indication	171
Wrong outcome	0
Number of citations retrieved	*8*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	2
Wrong intervention	0
Wrong comparator	0
Wrong indication	2
Wrong outcome	0
Not in English	1
Number of citations included	*3*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*1002*
Initial number of citations (Cochrane Library)	*319*
Number of duplicates	*41*
Citations retrieved from manual search	*6*
Number of citations searched by title/abstract	*1286*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	518
Wrong intervention	607
Wrong comparator	42
Wrong indication	1
Wrong outcome	45
Not in English	26
Number of citations retrieved	*47*
Full paper	
Not a clinical study	1
Wrong intervention	1
Wrong comparator	9
Wrong indication	0

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Wrong outcome	13
Not in English	0
Citations included in Level I evidence	*16*
Number of citations included	*5*

Intervention 7 – Point-of-care testing using thromboelastography

LEVEL I-IV EVIDENCE: ALL STUDY TYPES	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*1921*
Initial number of citations (Cochrane Library)	*307*
Number of duplicates	*40*
Number of citations searched by title/abstract	*2188*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	157
Wrong intervention	2001
Wrong comparator	0
Wrong indication	0
Wrong outcome	13
Number of citations retrieved	*17*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	0
Wrong intervention	10
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Not in English	0
Number of citations included	*7*

Intervention 8 – Administration of antifibrinolytics & DDAVP

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*388*
Initial number of citations (Cochrane Library)	*106*
Number of duplicates	*56*
Number of citations searched by title/abstract	*438*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	243
Wrong intervention/comparator	84
Wrong indication	59
Wrong outcome	2
Not a SR	3
Other[a]	1
Not in English	2
Number of citations retrieved	*44*
Citations retrieved from manual search	*3*
Full paper	
Not a clinical study	8
Wrong intervention/comparator	2
Wrong indication	0
Wrong outcome	1
Not a SR	3
Other[b]	3
Number of citations included	*30*

[a] Other = review does not exist.
[b] Other = data not pooled x 3.

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS (APROTININ)	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*301*
Initial number of citations (Cochrane Library)	*49*
Number of duplicates	*50*
Number of citations searched by title/abstract	*300*
Title/abstract	
Not a clinical study	201
Wrong intervention/comparator	53
Wrong indication	1
Wrong outcome	6
Not an RCT	22
Other[a]	3
Not in English	3
Number of citations retrieved	*11*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	0
Wrong intervention/comparator	0
Wrong indication	2
Wrong outcome	0
Not an RCT	0
Other[b]	2
Number of citations included	*7*

[a] Other = abstract only x 2; < 10 patients per treatment arm.
[b] Other = abstract only; < 10 patients per treatment arm.

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS (TRANEXAMIC ACID AND E-AMINOCAPROIC ACID)	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*321*
Initial number of citations (Cochrane Library)	*78*
Number of duplicates	*59*
Number of citations searched by title/abstract	*340*
Title/abstract	
Not a clinical study	221
Wrong intervention/comparator	53
Wrong indication	18
Wrong outcome	0
Not an RCT	9
Not in English	7
Number of citations retrieved	*32*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	0
Wrong intervention/comparator	0
Wrong indication	1
Wrong outcome	0
Not an RCT	2
Other[a]	11
Number of citations included	*18*

[a] Other = abstract only x 8; duplicate data x 2; < 10 patients per treatment arm.

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS (DESMOPRESSIN)	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*78*
Initial number of citations (Cochrane Library)	*17*
Number of duplicates	*3*
Number of citations searched by title/abstract	*92*
Title/abstract	
Not a clinical study	66
Wrong intervention/comparator	8
Wrong indication	18
Wrong outcome	0
Not an RCT	0
Not in English	0
Number of citations retrieved	*0*
Citations retrieved from manual search	*0*
Number of citations included	*0*

Intervention 9 – Appropriate patient positioning

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*1641*
Initial number of citations (Cochrane Library)	*6*
Number of duplicates	*52*
Citations retrieved from manual search	*0*
Number of citations searched by title/abstract	*1589*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	95
Wrong intervention	1413
Wrong comparator	0
Wrong indication	34
Wrong outcome	43
Number of citations retrieved	*14*
Full paper	
Not a clinical study	2
Wrong intervention	0
Wrong comparator	0
Wrong indication	1
Wrong outcome	3
Not in English	2
Number of citations included	*6*

Intervention 10 – Preoperative autologous donation

LEVEL I EVIDENCE: SYSTEMATIC REVIEWS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*479*
Initial number of citations (Cochrane Library)	*146*
Number of duplicates	*2*
Number of citations searched by title/abstract	*623*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	167
Wrong intervention	445
Wrong comparator	0
Wrong indication	1
Wrong outcome	0
Number of citations retrieved	*10*
Citations retrieved from manual search	*0*
Full paper	
Not a clinical study	0
Wrong intervention	2
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Not a SR	0
Number of citations included	*8*

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*927*
Initial number of citations (Cochrane Library)	*147*
Number of duplicates	*56*
Number of citations searched by title/abstract	*1018*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	463
Wrong intervention	524
Wrong comparator	5
Wrong indication	0
Wrong outcome	0
Not an RCT	22
Not in English	3
Number of citations retrieved	*1*
Citations retrieved from manual search	*1*
Full paper	
Not a clinical study	0
Wrong intervention	0
Wrong comparator	0

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Wrong indication	0
Wrong outcome	0
Not in English	0
Not an RCT	0
Number of citations included	*2*

Perioperative Question 3 – Quality of life

LEVEL II EVIDENCE: RANDOMISED CONTROLLED TRIALS	
REASON FOR EXCLUSION	NUMBER OF CITATIONS EXCLUDED
Initial number of citations (EMBASE.com)	*1173*
Initial number of citations (Cochrane Library)	*NA* [a]
Number of duplicates	*0*
Number of citations searched by title/abstract	*1173*
Non-duplicate citations identified in CINAHL & AMI	*0*
Title/abstract	
Not a clinical study	375
Wrong intervention	798
Wrong comparator	0
Wrong indication	0
Wrong outcome	0
Number of citations retrieved	*0*
Citations retrieved from manual search	*0*

[a] The clinical trials database in the Cochrane Library does not contain Level III and Level IV evidence

Appendix D: Evidence matrixes

Evidence matrixes are presented below for each intervention within Perioperative Question 3. A separate evidence statement form is shown for each primary outcome and also any of the secondary outcomes that were co-reported. Each evidence statement form is accompanied by an evidence summary table which summarises the evidence base for that particular outcome.

For each intervention, the complete set of evidence statement forms is followed by a separate form that contains any recommendations which were formulated from the evidence base for that intervention.

Intervention 1 – Acute normovolemic haemodilution

Key question(s): In patients undergoing surgery, what is the effect of ANH on transfusion incidence?		Evidence table ref*: POQ3.I1.P1
1. Evidence base		
Level I evidence: Carless 2004 (fair quality[1]; 25 trials, N=1081; adults undergoing any type of surgery) and Gurusamy 2009 (good quality, 3 trials, N=233; adults undergoing liver resection). Level II evidence published after the Carless 2004 literature search: 12 RCTs: Bennett 2006 (fair quality; N=155); Casati 2002 (poor quality; N=204); Casati 2004 (fair quality; N=100); Friesen 2006 (fair quality; N=32); Hohn 2002 (poor quality; N=80); Jarnagin 2008 (fair quality; N=130); Juelsgaard 2002 (fair quality; N=28); Lim 2003 (fair quality; N=30); Matot 2002 (fair quality; N=78); Sanders 2004 (fair quality; N=160); Saricaoglu 2005 (good quality[2]; N=30); Wolowczyk 2003[3] (fair quality; N=36).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The meta-analysis conducted herein showed a significant degree of heterogeneity (P< 0.0001; I^2=83%). The heterogeneity remains significant when assessed by surgery type.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Meta-analysis of systematic review and 11 of the 12 RCTs (except Wolowczyk 2003); Patients transfused with allogeneic blood; see Technical Report. All surgery types – RR 0.71 (0.61, 0.84); 37 trials; N=2098 Cardiac surgery – RR 0.84 (0.70, 1.02); 14 trials; N=940 Orthopaedic surgery – RR 0.76 (0.58, 1.00); 9 trials; N=467 Miscellaneous surgery[4] – RR 0.57 (0.43, 0.76); 14 trials; N=691 Results from Gurusamy 2009 (liver resection): RR 0.41 (0.25, 0.66); 3 trials; N=233	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. The studies were conducted in adults undergoing cardiac, orthopaedic, liver and other surgeries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Most of the studies were conducted in developed countries (UK, USA, Germany, France, Sweden, Turkey, Taiwan, Belgium, Egypt, South Africa, Israel). Boussofara 2002 (from the Carless 2004 systematic review) was conducted in Tunisia, but the exclusion of this study does not impact on the result. None of the studies were conducted in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Carless 2004 did not report the quality of the included studies; however, Bryson 1998 conducted a quality assessment 16 of the 25 RCTs included in Carless 2004. All 16 RCTs would be considered fair or poor quality.

Friesen 2006 was not taken into account as the study was in infants.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level I studies and several Level II studies with moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	ANH moderately reduces the incidence of allogeneic blood transfusion
4. Generalisability	B	Evidence directly generalisable to target population with some caveats. Surgery types assessed include cardiac, orthopaedic, liver resection, and others.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, ANH reduces the incidence of allogeneic blood transfusion.

Abbreviations: ANH, acute normovolemic haemodilution; het, heterogeneity; RCT, randomised controlled trial; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] No quality assessment of included studies were undertaken, the characteristics of the individual studies were appropriately summarised, the sources of heterogeneity were not sufficiently explored.

[2] Allocation to treatment groups was concealed from those responsible for recruiting subjects, patient characteristics and demographics were similar between treatment arms at baseline, all randomised patients were included in the analysis, the statistical methods were appropriate, and a transfusion protocol was reported. The study was not double-blinded.

[3] Study assesses transfusion incidence of banked autologous blood rather than allogeneic blood.

[4] Including cystectomy (Atallah 1993), prostatectomy (Boldt 1999), prostate resection (Malinovsky 1989), maxillofacial surgery (Bonnet 1986), Cervicofacial and ENT surgery (Boussofara 2002), liver resection (Jarnagin 2008; Matot 2002; von Bormann 1986), spinal surgery (Lim 2003), thoracic surgery (Moyes 1985), surgery for cancer (Rose 1981), gastrointestinal surgery (Sanders 2004), and any surgery type (Khanna 1998).

POQ3.I1.P1 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on transfusion incidence.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2004)	Level I *Fair*	25 trials (quality NR[1]) N=1081	Adults undergoing any type of surgery	All the studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH	Incidence of allogeneic blood transfusion	RR (95% CI): 0.69 (0.56, 0.84)		P<0.05	P<0.00001
Bennett (2006)	Level II *Fair*	N=155	Adults undergoing elective hip surgery.[2] Anticipated blood loss between 1 to 1.5 L	Hospital in UK	Autologous blood was collected immediately before surgery, aiming to reduce haemoglobin concentration to a target of 110 g per L. All autologous blood was returned within 6 hours of collection, starting on wound closure or sooner if a transfusion trigger was reached.	Incidence of allogeneic blood transfusion	15/78 (19%)	22 /77(29%)	P=0.18	
Casati (2002)	Level II *Poor*	N=204	Adults undergoing cardiac surgery[3]	Hospital in Italy	Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions.	Incidence of allogeneic blood (including PRBC, FFP, and PLTC) transfusion	35/103 (34%)	36/101 (36%)	P=0.88	
						Incidence of PRBC transfusion	32/103 (31%)	34/101 (34%)	P=0.47	
Casati (2004)	Level II *Fair*	N=100	Adults undergoing off-CPB CABG	Hospital in Italy	ANH with tranexamic acid (with tranexamic acid as control)	Incidence of PRBC transfusion	2/50 (4%)	10/50 (20%)	P=0.028	
						Incidence of allogeneic blood transfusion (including PRBC, FFP, and PLTC)	2/50 (4%)	10/50 (20%)	P=0.028	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Friesen (2006)	Level II *Fair*	N=32	Infants undergoing non-complex open cardiac surgery	Hospital in USA	ANH: 15 mL/kg whole blood withdrawn from the patient through the central venous catheter. Isovolemia was maintained by infusion of 1 mL of 5% albumin solution for each mL of blood withdrawn. Autologous blood retransfused postoperatively.	Incidence of FFP or platelet transfusion	1/16 (6.2%)	5/16 (31%)	P=0.06	
Hohn (2002)	Level II *Poor*	N=80	Adults undergoing on-CPB cardiac surgery	Hospital in Switzerland	ANH from a mean haematocrit of 43% to 28%.	Incidence of allogeneic blood transfusion	12/39 (31%)	12/41 (29%)	P=0.88	
Jarnagin (2008)	Level II *Fair*	N=130	Adults undergoing major hepatic resection (three or more liver segments) for any diagnosis, with or without any other planned procedures	Hospital in USA	ANH: blood was withdrawn to a target haemoglobin concentration of 8.0 g/dL, with a maximum of 3 L of blood removed. Normovolemia was maintained by replacing half of the removed blood volume with 5% albumin and the other half with crystalloid.	Patients undergoing any allogeneic transfusion	14/63 (22.2%)	23/67 (34%)	P=0.13	
						Incidence of allogeneic RBC transfusion (total)	8/63 (12.7%)	17/67 (25.4%)	P=0.08	
						Incidence of allogeneic RBC transfusion (intraoperative)	1/63 (1.6%)	7/67 (10.4%)	P=0.07	
						Incidence of FFP transfusion	11/63 (17.5%)	19/67 (28.4%)	P=0.15	
Juelsgaard (2002)	Level II *Fair*	N=28	Adults undergoing TKA	Hospital in Denmark	20% of the total blood volume was drawn before anaesthesia. This volume was simultaneously replaced with an equal volume of HES 6%. Blood re-transfusion was completed within 6 h.	Incidence of PRBC transfusion	7/14 (50%)	6/14 (43%)	P=0.71	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Lim (2003)	Level II *Fair*	N=30	Adults undergoing spinal surgery	Hospital in South Korea	ANH and esmolol-induced controlled hypotension (E-ANH group): for ANH autologous blood was withdrawn from the radial artery aiming for 28% haematocrit. To maintain normovolemia, the first 500 mL of blood drawn was simultaneously replaced with an equal amount of 6% HES, and the blood thereafter was replaced with three times that volume of Lactated Ringer's solution.	Incidence of PRBC transfusion	10/15 (67%)	15/15 (100%)	P=0.04	
Matot (2002)	Level II *Fair*	N=78	Adults undergoing liver resection	Hospital in Israel	ANH: Preoperatively, blood was transfused from the patients into standard citrate-phosphate-dextrose blood storage bags, and was simultaneously replaced by colloid solutions. The volume of blood collected was 2,020 ± 412 mL.	Incidence of PRBC transfusion	4/39 (10%)	14/39 (36%)	P=0.014	
Sanders (2004)	Level II *Fair*	N=160	Adults undergoing major gastrointestinal surgery (colorectal, gastric, or pancreatic)[4]	Hospital in UK	Maximum 3 units of blood withdrawn and transfused into blood bags containing citrate-phosphate-dextrose (anticoagulant). Warmed cell-free fluid was administered during blood withdrawal to maintain normovolemia. At the end of the operation, all the autologous blood was re-transfused.	Incidence of allogeneic blood transfusion	22/78 (28%)	25/82 (30%)	P=0.75	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Saricaoglu (2005)	Level II *Good*	N=30	Adults undergoing hip arthroplasty	Hospital in Turkey	ANH: autologous blood 15 mL/kg was withdrawn and replaced by ~15mL/kg 6% HES HHD: 15 mL/kg HES administered without removal of any autologous blood Control: no haemodilution	Incidence of allogeneic blood transfusion	2/10 (20%)	HDD: 4/10 (40%) Control: 10/10 (100%)	ANH vs. HHD P=0.35 ANH vs. control P=0.01	
Wolowczyk (2003)	Level II *Fair*	N=36	Adults undergoing abdominal aortic aneurysm repair	Hospital in UK	ANH and cell salvage: 15 g/kg of blood was withdrawn and replaced with a similar volume of 6% HES Control: standard care (including cell salvage)	Intraoperative transfusion of banked autologous blood	7/16 (44%)	7/18 (39%)	P=0.77	
						Postoperative transfusion of banked autologous blood	5/16 (31%)	10/18 (56%)	P=0.18	
						Total transfusion of banked autologous blood	10/16 (63%)	13/18 (72%)	P=0.55	
Cardiac surgery										
Carless (2004)	Level I *Fair*	10 trials (quality NR) N=NR	Adult patients undergoing any type of surgery	All studies conducted in developed countries	ANH	Incidence of allogeneic blood transfusion	RR (95% CI): 0.77 (0.57, 1.04)		P>0.05	Phet=NR
Orthopaedic surgery										
Carless (2004)	Level I *Fair*	6 trials (quality NR) N=NR	Adult patients undergoing any type of surgery	All studies conducted in developed countries	ANH	Incidence of allogeneic blood transfusion	RR (95% CI): 0.79 (0.60, 1.06)		P>0.05	Phet=NR

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Liver resection										
Gurusamy (2009)	Level I *Fair*	3 trials (fair quality) N=233	Patients undergoing liver resection[5]	The RCTs were conducted in USA, Israel, and China.	ANH	Incidence of allogeneic blood transfusion	RR (95% CI): 0.41 (0.25, 0.66)		P<0.05	Phet=NR
Miscellaneous										
Carless (2004)	Level I *Fair*	9 trials (quality NR) N=NR	Adult patients undergoing any type of surgery	All studies conducted in developed countries	ANH	Incidence of allogeneic blood transfusion	RR (95% CI): 0.42 (0.24, 0.74)		P<0.05	
Transfusion protocol used										
Carless (2004)	Level I *Fair*	16 trials (quality NR) N=NR	Adult patients undergoing any type of surgery	All studies conducted in developed countries	ANH	Incidence of allogeneic blood transfusion	RR (95% CI): 0.81 (0.62, 1.00)		P=0.05	
No transfusion protocol used										
Carless (2004)	Level I *Fair*	9 trials (quality NR) N=NR	Adult patients undergoing any type of surgery	All studies conducted in developed countries	ANH	Incidence of allogeneic blood transfusion	RR (95% CI): 0.53 (0.36, 0.76)		P<0.05	

Abbreviations: ANH, acute normovolemic haemodilution; CABG, coronary artery bypass surgery; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; HES, hydroxyethyl starch; HHD, hypervolemic haemodilution; NR, not reported; PLTC, platelet concentration; PRBC, packed red blood cells; RCT, randomised controlled trial; TKA, total knee arthroplasty.

[1] Bryson 1998 reported the quality of 16 of the 25 studies included in Carless 2004 that reported this outcome. Three studies had a Jadad score of 2 and the rest had a Jadad score of 1. Seven studies reported a transfusion protocol. Two studies (Triulzi 1995 and Von Bormann 1986) with a Jadad score of 2 reported the use of a transfusion protocol. Full texts of these two papers were retrieved. Triulzi 1995 was considered to be fair quality (not double-blinded, no allocation concealment reported, demographics similar between groups, all randomised patients included in analysis, statistical methods appropriate). Von Bormann 1986 was in German and therefore its quality was not assessed further. The other 14 studies in Bryson 1998 would have been rated as either fair or poor based on the Jadad scores and whether or not a transfusion protocol was reported.

[2] Most patients underwent primary total hip replacement, with 15 revision hip arthroplasties (seven in ANH and eight in standard transfusion) and one hip resurfacing procedure.

[3] Procedures included single and multiple valve surgery, aortic root surgery, coronary surgery combined with valve surgery, or partial left ventriculectomy.

[4] These operations were considered high risk (>40%) for allogeneic transfusion.

[5] Trials were included irrespective of whether they included major or minor liver resections, normal or cirrhotic livers, vascular occlusion was used or not, and irrespective of the reason for liver resection.

Key question(s): In patients undergoing surgery, what is the effect of ANH on transfusion volume?			Evidence table ref*: POQ3.I1.P2
1. Evidence base			
Level I evidence: Carless 2004 (fair quality[1]; 17 trials, N=NR; adults undergoing any type of surgery) and Gurusamy 2009 (good quality; 2 trials, N=150; adults undergoing liver resection) Level II evidence: 11 trials: Aklagh 2007 (poor quality; N=60); Bennett 2006 (fair quality; N=155); Casati 2002 (poor quality; N=204); Casati 2004 (fair quality, N=100); Hohn 2002 (poor quality; N=80); Jarnagin 2008 (fair quality; N=130); Juelsgaard 2002 (fair quality; N=28); Lim 2003 (fair quality; N=30); Sanders 2004 (fair quality; N=160); Saricaoglu 2005 (good quality[2]; N=30); Wolowczyk 2003 (fair quality; N=36)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency			
Carless 2004 did not report the level of heterogeneity. The results from Carless 2004 are not consistent with many of the subsequently published RCTs. Gurusamy 2009 found a significant degree of heterogeneity between trials of adults undergoing liver resection. There was a significant degree of heterogeneity in the meta-analysis conducted herein (P<0.0001; I^2= 79% for all surgery types).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
w Clinical impact			
A meta-analysis was conducted herein using results from the RCTs reported in Carless 20043 and the subsequently published RCTs that reported sufficient information to be included in the analysis (Jarnagin 2008; Lim 2003; Saricaoglu 2005); see Technical Report. General – mean difference (unit) -0.90 (-1.22, -0.57); 16 trials; N=817 Cardiac surgery – mean difference -1.00 (-1.48, -0.52); 10 trials; N=537 Orthopaedic surgery – mean difference -0.61 (-1.39, 0.18); 3 trials; N=70 Miscellaneous surgery – mean difference -1.14 (-2.57, 0.30); 3 trials; N=210	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
4. Generalisability			
The evidence is generalisable to an adult population who are undergoing elective surgery. The studies were conducted in adults undergoing cardiac, orthopaedic, liver and other surgeries.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability			
The studies were conducted in a wide range of countries (Germany, USA, Belgium, India, Turkey, South Africa, Israel, Taipei, UK, China, Italy, Switzerland, Denmark, South Korea, Iran). All the studies were in a hospital setting. None of the studies were conducted in Australia.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors

Carless 2004 did not report the quality of the included studies; however, Bryson 1998 conducted a quality assessment 13 of the 17 RCTs included in Carless 2004. All 13 RCTs would be considered fair or poor quality.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level I studies and several Level II studies with moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	C	ANH moderately reduces the volume of allogeneic blood transfusion
4. Generalisability	B	Evidence directly generalisable to target population with some caveats. Surgery types assessed include cardiac, orthopaedic, liver resection, and others.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, ANH may reduce the volume of allogeneic blood transfusion.

Abbreviations: ANH, acute normovolemic haemodilution; NR, not reported; RCT, randomised controlled trial

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] No quality assessment of included studies were undertaken, the characteristics of the individual studies were appropriately summarised, the sources of heterogeneity were not sufficiently explored.

[2] Allocation to treatment groups was concealed from those responsible for recruiting subjects, patient characteristics and demographics were similar between treatment arms at baseline, all randomised patients were included in the analysis, the statistical methods were appropriate, and a transfusion protocol was reported. The study was not double-blinded.

[3] Carless 2004 did not provide sufficient detail for the meta-analysis; therefore the original RCTs were sourced. Lilleaasen (1977) was not included because the study comparator was low volume ANH; Von Borman 1986 was excluded because the study was not in English; and Vedrinne 1992 was excluded due to insufficient detail.

POQ3.I1.P2 Characteristics and results of studies examining the effect of ANH on transfusion volume.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Carless (2004)	Level I *Fair*	17 trials (quality NR[1]) N=NR	Adults undergoing any type of surgery	All studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH	Mean difference (95% CI) in units of allogeneic blood transfused	-1.9 (-2.7, -1.1)		P<0.05
Gurusamy (2009)	Level I *Good*	2 trials (fair quality) N=150	Patients undergoing liver resection[2]	Studies conducted in USA, Israel, and China.	ANH	Mean difference (95% CI) in units of RBCs transfused	-0.09 (-0.48, 0.29)		P>0.05
Akhlagh (2007)	Level II *Poor*	N=60	Adults undergoing on-CPB CABG	Hospital in Iran	ANH and re-transfusion of autologous blood after separating the patient from the cardiopulmonary machine.	Mean (SD) volume of allogeneic blood transfused, mL	870 (NR)	2010 (NR)	P=0.024
Bennett (2006)	Level II *Fair*	N=155	Adults undergoing elective hip surgery. Anticipated blood loss between 1 to 1.5 L.	Hospital in UK	Autologous blood was collected immediately before surgery, aiming to reduce Hb concentration to a target of 110 g per L. All autologous blood was returned within 6 hours of collection, starting on wound closure or sooner if a transfusion trigger was reached.	Mean (SD) units of allogeneic blood transfused	2.2 (NR)	2.9 (NR)	NR
Casati (2002)	Level II *Poor*	N=204	Adults undergoing cardiac surgery[3]	Hospital in Italy	Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions.	Mean (SD) units of PRBCs transfused	3.8 (NR)	3.7 (NR)	P=0.47
Casati (2004)	Level II *Fair*	N=100	Adults undergoing off-CPB CABG	Hospital in Italy	ANH with tranexamic acid (with tranexamic acid as control)	Mean (SD) units of PRBCs transfused	2.5 (NR)	2.4 (NR)	P<0.001
Hohn (2002)	Level II *Poor*	N=80	Adults undergoing on-CPB cardiac surgery	Hospital in Switzerland	ANH from a mean haematocrit of 43% to 28%.	Median (range) units of allogeneic blood transfused	2 (1 to 5)	2 (1 to 3)	P=0.219
Jarnagin (2008)	Level II *Fair*	N=130	Adults undergoing major hepatic resection (three or more liver segments) for any diagnosis, with	Hospital in USA	ANH: blood was withdrawn to a target Hb concentration of 8.0 g/dL, with a maximum of 3 L of	Mean (SE) units of allogeneic PRBC transfused	3.5 (1.3)	2.1 (0.5)	P=0.6

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
			or without any other planned procedures		blood removed. Euvolemia was maintained by replacing half of the removed blood volume with 5% albumin and the other half with crystalloid.	Mean (SE) units of any allogeneic transfusion (PRBC or FFP)	5.6 (1.7)	6.9 (2.7)	P=0.72
Juelsgaard (2002)	Level II *Fair*	N=28	Adults undergoing TKA	Hospital in Denmark	20% of the total blood volume was drawn before anaesthesia. This volume was simultaneously replaced with an equal volume of HES 6%. Blood re-transfusion was completed within 6 h.	Mean (SD) volume of allogeneic blood transfused, mL	386	343	P=0.85
Lim (2003)	Level II *Fair*	N=30	Adults undergoing spinal surgery	Hospital in South Korea	ANH and esmolol-induced controlled hypotension (E-ANH group): for ANH autologous blood was withdrawn from the radial artery aiming for 28% haematocrit. To maintain normovolemia, the first 500 mL of blood drawn was simultaneously replaced with an equal amount of 6% HES, and the blood thereafter was replaced with three times that volume of Lactated Ringer's solution.	Mean (SE) units of PRBCs transfused	2.2 (2.3)	4.3 (1.5)	P<0.01
Sanders (2004)	Level II *Fair*	N=160	Adults undergoing major gastrointestinal surgery (colorectal, gastric, or pancreatic)[4]	Hospital in UK	ANH: Maximum 3 units of blood withdrawn preoperatively and replaced with warmed cell-free fluid to maintain normovolemia. At the end of the operation, all the autologous blood was re-transfused.	Mean (SD) units of allogeneic blood transfused	4.1 (NR)	3.7 (NR)	P>0.05
Saricaoglu (2005)	Level II *Good*	N=30	Adults undergoing hip arthroplasty	Hospital in Turkey	ANH: autologous blood 15 mL/kg was withdrawn and replaced by ~15mL/kg 6% HES HHD: 15 mL/kg HES administered without removal of any autologous blood Control: no haemodilution	Mean (SD) units of allogeneic PRBCs transfused	1.5 (0.7)	HHD: 1.25 (0.5) Control: 1.3 (0.5)	ANH vs. HHD P=0.33 ANH vs. Control P=0.33

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Wolowczyk (2003)	Level II *Fair*	N=36	Adults undergoing abdominal aortic aneurysm repair	Hospital in UK	ANH and cell salvage: 15 g/kg of blood was withdrawn and replaced with a similar volume of 6% HES Control: standard care (including cell salvage)	Median (IQR) units of allogeneic blood transfused intraoperatively	0 (0 to 4)	0 (0 to 2)	P=0.51
						Median (IQR) units of allogeneic blood transfused postoperatively	0 (0 to 2)	1 (0 to 2)	P=0.33
						Median (IQR) units of allogeneic blood transfused intra- and postoperatively	2 (0 to 5)	2.5 (0 to 5)	P=0.68
Carless (2004)	Level I *Fair*	NR	Adults undergoing any type of surgery	All studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH	Mean difference (95% CI) in units of allogeneic blood transfused.	-1.0 (-1.7, -0.4)		P<0.05
Carless (2004)	Level I *Fair*	NR	Adults undergoing any type of surgery	All studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH	Mean difference (95% CI) in units of allogeneic blood transfused.	-3.0 (-4.9, -1.1)		P<0.05

Abbreviations: ANH, acute normovolemic haemodilution; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Hb, haemoglobin; HES, hydroxyethyl starch; het, heterogeneity; HHD, hypervolemic haemodilution; IQR, interquartile range; NR, not reported; PRBC, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TKA, total knee arthroplasty.

[1] Bryson 1998 reported the quality of 13 of the 17 studies included in Carless 2004 that reported this outcome. Five studies had a Jadad score of 2 and the rest had a Jadad score of 1. Six studies reported the use of a transfusion protocol. Three studies (Kochamba 1996, Triulzi 1995, and Von Borman 1986) with a Jadad score of 2 reported the use of a transfusion protocol. Full texts of these three papers were retrieved. Kochamba 1996 and Triulzi 1995 were considered to be fair quality (not double-blinded, no allocation concealment reported, demographics similar between groups, all randomised patients included in analysis, statistical methods appropriate). Von Bormann 1986 was in German and therefore its quality was not assessed further. The other 10 studies in Bryson 1998 would have been rated as either fair or poor based on the Jadad scores and whether or not a transfusion protocol was reported.

[2] Trials were included irrespective of whether they included major or minor liver resections, normal or cirrhotic livers, vascular occlusion was used or not, and irrespective of the reason for liver resection.

[3] Most patients underwent primary total hip replacement, with 15 revision hip arthroplasties (seven in ANH and eight in standard transfusion) and one hip resurfacing procedure.

[4] These operations were considered high risk (>40%) for allogeneic transfusion.

Key question(s): In patients undergoing surgery, what is the effect of ANH on blood loss?		Evidence table ref*: POQ3.I1.P3
1. Evidence base		
Level I evidence: Bryson 1998 (good quality; 13 trials, all fair to poor quality, N=500; any surgery type) and Gurusamy 2009 (good quality; 2 trials; N=98; adults undergoing liver resection) Level II evidence: 11 RCTs: Bennett 2006 (fair quality; N=155); Casati 2002 (poor quality; N=204); Casati 2004 (fair quality; N=100); Friesen 2006 (fair quality; N=32); Jarnagin 2008 (fair quality; N=130); Juelsgaard 2002 (fair quality; N=28); Lim 2003 (fair quality; N=30); Matot 2002 (fair quality; N=78); Sanders 2004 (fair quality; N=160); Saricaoglu 2005 (good quality[1]; N=30); Wolowczyk 2003 (fair quality; N=36)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Within Bryson 1998, five studies found that ANH was associated with a significant decrease in blood loss and eight studies found no significant difference. The degree of heterogeneity in the Bryson 1998 studies is statistically significant (P<0.001). The meta-analysis in Bryson 1998 found a small, but statistically significant impact in the trials with patients undergoing cardiac surgery but not trials of patients undergoing orthopaedic surgery or other surgery types. Of the RCTs published after Bryson 1998, two found a significant association between ANH and decreased blood loss and the other nine studies found no statistically significant association	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Results from Bryson 1998 All surgery types – mean difference -117 mL (-292, 58); 13 trials; N=500 Cardiac surgery – mean difference -233 mL (-459, -5); 7 trials; N=350 (of the two RCTs published subsequently, only one reported lower blood loss in the intervention arm, and neither reported a significant difference) Orthopaedic surgery – mean difference 33 mL (-512, 578); 1 trial; N=31 Miscellaneous surgery – mean difference -97 mL (-339, 145); 5 trials; N=119 Results from Gurusamy 2009 (liver resection) – mean difference 1.53 (-102, 105); 2 trials; N=98 Results from Level II studies – see evidence summary table POQ3.I1.P3	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. The studies were conducted in adults undergoing cardiac, orthopaedic, liver and other surgeries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability		
The studies in Bryson 1998 were conducted in Europe with the exception of two studies conducted in USA and one in South Africa. The studies in Gurusamy 2009 were conducted in Israel and China. The RCTs not included in either Bryson 1998 or Gurusamy 2009 were conducted in UK, Italy, USA, Denmark, South Korea, and Turkey.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Although Bryson 1998 was a good quality systematic review, all the included RCTs were fair to poor quality.

Friesen 2006 was not taken into account as the study was in infants.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two good quality Level I studies and several Level II studies with moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	D	No statistically significant impact
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on blood loss is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; RCT, randomised controlled trial

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] Allocation to treatment groups was concealed from those responsible for recruiting subjects, patient characteristics and demographics were similar between treatment arms at baseline, all randomised patients were included in the analysis, the statistical methods were appropriate, and a transfusion protocol was reported. The study was not double-blinded.

POQ3.I1.P3 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on blood loss.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Bryson (1998)	Level I *Good*	13 trial (fair and poor quality[1]) N=500	Adults undergoing any surgery type	All studies conducted in developed countries	ANH	Mean difference (95% CI) in perioperative blood loss, mL	-117 (-292, 58)		P>0.05	Phet<0.001
Bennett (2006)	Level II *Fair*	N=155	Adults undergoing elective hip surgery.1 Anticipated blood loss between 1 to 1.5 L.	Hospital in UK	Autologous blood collected immediately before surgery, aiming to reduce Hb concentration to a target of 110 g per L. All autologous blood returned within 6 hours of collection, starting on wound closure or sooner if a transfusion trigger was reached.	Median (IQR) intraoperative blood loss, mL	692 (452, 1019)	641 (477, 1007)	P=0.82	
						Median (IQR) total blood loss, mL	1182 (840, 1646)	1210 (816, 1545)	P=0.82	
Casati (2002)	Level II *Poor*	N=204	Adults undergoing cardiac surgery[2]	Hospital in Italy	Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions.	Median (IQR) bleeding 0-4 hours after surgery, mL	158 (106, 305)	172 (117.5, 265)	P=0.93	
						Mean (IQR) total postoperative bleeding (mL)	374 (255, 704)	412 (313, 552)	P=0.94	
Casati (2004)	Level II *Fair*	N=100	Adults undergoing off-CPB CABG	Hospital in Italy	ANH with tranexamic acid (with tranexamic acid as control)	Median (IQR) bleeding 0-4 hours after surgery, mL	160 (110, 235)	150 (100, 220)	NS	
						Mean (IQR) total postoperative bleeding (mL)	375 (248, 475)	350 (300, 443)	NS	
Friesen (2006)	Level II *Fair*	N=32	Infants undergoing non-complex open cardiac surgery	Hospital in USA	ANH: 15 mL/kg whole blood withdrawn through the central venous catheter. Normovolaemia was maintained by infusion of 1 mL of 5% albumin solution for each mL of blood withdrawn. Autologous blood re-transfused postoperatively.	Postoperative 24 hour blood loss	NR	NR	Was less in the treatment group when measured as mL per 24 h (P=0.036), but not significantly less when measured as mL/kg.24h (P=0.16).	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Jarnagin (2008)	Level II *Fair*	N=130	Adults undergoing major hepatic resection (three or more liver segments) for any diagnosis, with or without any other planned procedures.	Hospital in USA	ANH: blood withdrawn to a target Hb concentration of 8.0 g/dL, with a maximum of 3 L of blood removed. Normovolaemia was maintained by replacing half of the removed blood volume with 5% albumin and the other half with crystalloid.	Mean (range) blood loss, mL	800 (100 to 3200)	700 (100 to 4000)	P=0.42	
Juelsgaard (2002)	Level II *Fair*	N=28	Adults undergoing TKA	Hospital in Denmark	20% of the total blood volume was drawn before anaesthesia and simultaneously replaced with an equal volume of HES 6%. Blood re-transfusion was completed within 6 h.	Mean (SD) intraoperative blood loss, mL	131 (78)	111 (56)	P=0.45	
						Mean (SD) total blood loss, mL	1306 (300)	1026 (294)	P=0.02	
Lim (2003)	Level II *Fair*	N=30	Adults undergoing spinal surgery	Hospital in South Korea	ANH and esmolol-induced controlled hypotension (E-ANH group): for ANH autologous blood was withdrawn from the radial artery aiming for 28% haematocrit. To maintain normovolaemia, the first 500 mL of blood drawn was simultaneously replaced with an equal amount of 6% HES, and the blood thereafter was replaced with three times that volume of Lactated Ringer's solution.	Mean (SD) volume of intraoperative bleeding, mL	1600 (620)	1500 (697)	P>0.05	
						Mean (SD) volume of postoperative bleeding, mL	600 (372)	883 (473)	P>0.05	
Matot (2002)	Level II *Fair*	N=78	Adults undergoing liver resection	Hospital in Israel	ANH: Preoperatively, blood was transfused from the patients into standard citrate-phosphate-dextrose blood storage bags, and was simultaneously replaced by colloid solutions. The volume of blood collected was 2,020 ± 412 mL.	Mean (SD) surgical blood loss (mL)	1442 (1827)	1528 (1822)	P=0.84	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Sanders (2004)	Level II *Fair*	N=160	Adults undergoing major gastrointestinal surgery (colorectal, gastric, or pancreatic)[3]	Hospital in UK	ANH: Maximum 3 units of blood withdrawn preoperatively and replaced with warmed cell-free fluid to maintain normovolaemia. At the end of the operation, all autologous blood was re-transfused.	Median (range) blood loss, mL	750-1000 (100-4500)	750-1000 (100-4368)	NR	
Saricaoglu (2005)	Level II *Good*	N=30	Adults undergoing hip arthroplasty	Hospital in Turkey	ANH: autologous blood 15 mL/kg was withdrawn and replaced by ~15mL/kg 6% HES HHD: 15 mL/kg HES administered without removal of any autologous blood Control: no haemodilution	Median (95% CI) intraoperative blood loss	740 (600, 830)	HHD: 650 (500, 855) Control: 695 (510, 855)	P=0.275	
Wolowczyk (2003)	Level II *Fair*	N=36	Adults undergoing abdominal aortic aneurysm repair	Hospital in UK	ANH and cell salvage: 15 g/kg of blood was withdrawn and replaced with a similar volume of 6% HES Control: standard care (including cell salvage)	Median (IQR) intraoperative blood loss, mL	1780 (930, 5000)	1700 (750, 2600)	P=0.55	
						Patients with blood loss below 1000 mL	4/16 (25%)	5/18 (28%)	P=1.0	
Cardiac surgery										
Bryson (1998)	Level I *Good*	7 trials (fair and poor quality[4]) N=350	Adults undergoing any surgery type	All studies conducted in developed countries	ANH	Mean difference (95% CI) in perioperative blood loss, mL	-233 (-459, -5)		P<0.05	Phet<0.001
Orthopaedic surgery										
Bryson (1998)	Level I *Good*	1 trial (fair/poor quality[5]) N=31	Adults undergoing any surgery type	All studies conducted in developed countries	ANH	Mean difference (95% CI) in perioperative blood loss, mL	33 (-512, 578)		P>0.05	Phet=NA

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Liver surgery										
Gurusamy (2009)	Level I *Good*	2 trials (fair quality) N=98	Patients undergoing liver resection[6]	Studies conducted in USA, Israel, and China.	ANH	Mean difference (95% CI) perioperative blood loss, mL	1.53 (-102, 105)		P>0.05	Phet=0.83
Miscellaneous surgery[7]										
Bryson (1998)	Level I *Good*	5 trials (fair and poor quality[8]) N=119	Adults undergoing any surgery type	All studies conducted in developed countries	ANH	Mean difference (95% CI) in perioperative blood loss, mL	-97 (-339, 145)		P>0.05	Phet=0.013

Abbreviations: ANH, acute normovolemic haemodilution; CABG; coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; Hb, haemoglobin; HES, hydroxyethyl starch; het, heterogeneity; HHD, hypervolemic haemodilution; IQR, interquartile range; NR, not reported; NS, not significant; SD, standard deviation; TKA, total knee arthroplasty.

[1] Three studies had a Jadad score of 2 and the other studies had a Jadad score of 1. Five studies reported the use of a transfusion protocol. Two studies (Kochamba 1996 and Triulzi 1995) with a Jadad score of 2 reported the use of a transfusion prootocl. Full texts of these two papers were retrived. Kochamba 1996 and Triulzi 1995 were considered to be fair quality (not double-blinded, no allocation concealment reported, demographics similar between groups, all randomised patients included in analysis, statistical methods appropriate). The other 11 studies in Bryson 1998 would have been rated as either fair or poor based on the Jadad scores and whether or not a transfusion protocol was reported.

[2] Procedures included single and multiple valve surgery, aortic root surgery, coronary surgery combined with valve surgery, or partial left ventriculectomy.

[3] These operations were considered high risk (>40%) for allogeneic transfusion.

[4] Two studies had a Jadad score of 2 and the other studies had a Jadad score of 1. Three studies reported the use of a transfusion protocol. Two studies (Kochamba 1996 and Triulzi 1995) with a Jadad score of 2 reported the use of a transfusion prootocl. Full texts of these two papers were retrived. Kochamba 1996 and Triulzi 1995 were considered to be fair quality (not double-blinded, no allocation concealment reported, demographics similar between groups, all randomised patients included in analysis, statistical methods appropriate). The other 5 studies in Bryson 1998 in this subgroup would have been rated as either fair or poor based on the Jadad scores and whether or not a transfusion protocol was reported.

[5] The study had a Jadad score of 1 and reported the use of a transfusion protocol.

[6] Trials were included irrespective of whether they included major or minor liver resections, normal or cirrhotic livers, vascular occlusion was used or not, and irrespective of the reason for liver resection.

[7] Including GI surgery (1 trial), thoracic surgery (1 trial), hepatic surgery (1 trial), ENT surgery (2 trials), urological surgery (2 trials), and vascular surgery (2 trials).

[8] One study had a Jadad score of 2 and the other studies had a Jadad score of 1. One study reported the use of a transfusion protocol. Neither of the studies with a Jadad score of 2 reported the use of a transfusion protocol. Therefore, all the studies in this subgroup would have been rated as either fair or poor based on the Jadad scores and whether or not a transfusion protocol was reported.

Key question(s): In patients undergoing surgery, what is the effect of ANH on mortality?		Evidence table ref*: POQ3.I1.P4
1. Evidence base		
Level I evidence: Carless 2004 (fair quality[1]; 8 trials, N=NR; adults undergoing any type of surgery) and Gurusamy 2009 (good quality; 2 trials, N=150; adults undergoing liver resection) **Level II evidence:** 6 RCTs: Bennett 2006 (fair quality; N=155); Casati 2002 (poor quality; N=204); Casati 2004 (fair quality; N=100); Hohn 2002 (poor quality; N=80); Matot 2002 (fair quality; N=78); Sanders 2004 (fair quality; N=160)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All the studies are consistent in finding no significant impact. However, studies are likely underpowered. Carless 2004 did not report heterogeneity.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable
3. Clinical impact		
Results from Carless 2004 – RR 1.16 (0.19, 7.15); 8 trials; N=NR Results from Gurusamy 2009 – RR 0.35 (0.04, 3.32); 2 trials; N=150 Results from Level II studies – see evidence summary table POQ3.I1.P4	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. The studies were conducted in adults undergoing cardiac, orthopaedic, liver and other surgeries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Included studies were underpowered to detect a mortality difference.

Quality of RCTs not reported in Carless 2004.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level I studies and several Level II studies with moderate risk of bias
2. Consistency	A	All studies consistent in finding no difference due to being underpowered
3. Clinical impact	D	No difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on mortality is uncertain.

Abbreviations; acute normovolemic haemodilution; NR, not reported; RCT, randomised controlled trial; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] No quality assessment of included studies were undertaken, the characteristics of the individual studies were appropriately summarised, the sources of heterogeneity were not sufficiently explored.

POQ3.I1.P4 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on mortality.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2004)	Level I *Fair*	8 trials (quality NR) N=NR	Adults undergoing any type of surgery	All studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH		RR (95% CI): 1.16 (0.19, 7.15)		P>0.05	Phet=NR
Gurusamy (2009)	Level I *Good*	2 trials (fair quality) N=150	Patients undergoing liver resection.[1]	Studies conducted in USA, Israel, and China.	ANH		RR (95% CI): 0.35 (0.04, 3.32)		P>0.05	Phet=1.00
Bennett (2006)	Level II *Fair*	N=155	Adults undergoing elective hip surgery.[2] Anticipated blood loss between 1 to 1.5 L.	Hospital in UK	Autologous blood was collected immediately before surgery, aiming to reduce Hb concentration to a target of 110 g per L. All autologous blood was returned within 6 hours of collection, starting on wound closure or sooner if a transfusion trigger was reached.		1/78 (1.3%)	0/77 (0%)	P=0.50	
Casati (2002)	Level II *Poor*	N=204	Adults undergoing cardiac surgery[1]	Hospital in Italy	Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions.		4/103 (3.9%)	4/101 (4%)	P=0.98	
Casati (2004)	Level II *Fair*	N=100	Adults undergoing off-CPB CABG	Hospital in Italy	ANH with tranexamic acid (with tranexamic acid as control)		0/50 (0%)	1/50 (2%)	P=0.50	
Hohn (2002)	Level II *Poor*	N=80	Adults undergoing on-CPB cardiac surgery	Hospital in Switzerland	ANH from a mean haematocrit of 43% to 28%.		0/39 (0%)	2/41 (5%)	P=0.31	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Matot (2002)	Level II *Fair*	N=78	Adults undergoing liver resection	Hospital in Israel	ANH: Preoperatively, blood was transfused into standard citrate-phosphate-dextrose blood storage bags, and was simultaneously replaced by colloid solutions. The volume of blood collected was 2,020 ± 412 mL.		0/39 (0%)	0/39 (0%)	Not estimable	
Sanders (2004)	Level II *Fair*	N=160	Adults undergoing major gastrointestinal surgery (colorectal, gastric, or pancreatic)[2]	Hospital in UK	ANH: Maximum 3 units of blood withdrawn preoperatively and replaced with warmed cell-free fluid to maintain normovolemia. At the end of the operation, all autologous blood was re-transfused.		2/78 (3%)	1/82 (1%)	P=0.54	

Abbreviations: ANH, acute normovolemic haemodilution; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; Hb, haemoglobin; het, heterogeneity; NR, not reported; RCT, randomised controlled trial; RR, relative risk.

[1] Trials were included irrespective of whether they included major or minor liver resections, normal or cirrhotic livers, vascular occlusion was used or not, and irrespective of the reason for liver resection.

[2] Procedures included single and multiple valve surgery, aortic root surgery, coronary surgery combined with valve surgery, or partial left ventriculectomy.

[3] These operations were considered high risk (>40%) for allogeneic transfusion.

Key question(s): In patients undergoing surgery, what is the effect of ANH on morbidity?		Evidence table ref*: POQ3.I1.P5
1. Evidence base		
Level I evidence: Carless 2004 (fair quality[1]) Infection (2 trials; N=NR); thrombosis (3 trials; N=NR); non-fatal MI (3 trials; N=NR) Gurusamy 2009 (good quality) Bile leak (1 trial; N=78); intra-abdominal bleeding (2 trials; N=208); intra-abdominal infection (1 trial; N=78); intra-abdominal collection req. drainage (1 trial; N=130); wound infection (2 trials; N=208); chest infection (1 trial; N=78) Level II evidence: 7 RCTs: Bennett 2006 (N=155; fair quality); Casati 2002 (N=204; poor quality); Casati 2004 (N=100; fair quality); Jarnagin 2008 (N=130; fair quality); Lim 2003 (N=30; fair quality); Matot 2002 (N=78; fair quality); Sanders 2004 (N=160; fair quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Most of the studies the studies are consistent in finding no significant impact of ANH on morbidity outcomes. In Bennet 2006, significantly fewer ANH patients had at least one significant postoperative complication (Bennet 2006 was the only study to report overall incidence as an outcome). Carless 2004 found that the incidence of thrombosis was significantly less in ANH patients. Carless 2004 did not report the degree of heterogeneity for the trials that reported thrombosis as an outcome. None of the RCTs published after Careless 2004 reported thrombosis as an outcome.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Results from Carless 2004 Infection – RR 4.94 (0.61, 40.19) Thrombosis – RR 0.44 (0.21, 0.93) Non-fatal MI – RR 3.43 (0.15, 79.74) Results from Gurusamy 2009 and Level II studies – see evidence summary table POQ3.I1.P5	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. The studies were conducted in adults undergoing cardiac, orthopaedic, liver and other surgeries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Thrombosis in Carless 2004 review was the only significant outcome but was not defined. As thrombosis was not adequately defined, the CRG did believe it was appropriate to make an evidence statement for this outcome.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level I studies and several Level II studies with low risk of bias
2. Consistency	C	Most studies consistent in finding no significant impact on morbidity
3. Clinical impact	D	A statistically significant impact on thrombosis with a confidence interval that includes clinically insignificant values. No statistically significant impact on other morbidity outcomes.
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on morbidity is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; NR, not reported; RCT, randomised controlled trial; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] No quality assessment of included studies were undertaken, the characteristics of the individual studies were appropriately summarised, the sources of heterogeneity were not sufficiently explored.

POQ3.I1.P5 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on morbidity.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2004)	Level I *Fair*	2 trials (quality NR) N=NR	Adults undergoing any type of surgery	All studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH	Infection	RR (95% CI): 4.94 (0.61, 40.19)		P>0.05	Phet=NR
		3 trials (quality NR) N=NR				Thrombosis	RR (95% CI): 0.44 (0.21, 0.93)		P<0.05	Phet=NR
		3 trials (quality NR) N=NR				Non-fatal MI	RR (95% CI): 3.43 (0.15, 79.74)		P>0.05	Phet=NR
Gurusamy (2009)	Level I *Good*	1 trial (fair quality) N=78	Patients undergoing liver resection.[1]	Studies conducted in USA, Israel, and China.	ANH	Bile leak	RR (95% CI): 1.5 (0.27, 8.49)		P>0.05	Phet=NA
		2 trials (fair quality) N=208				Intra-abdominal bleeding	RR (95% CI): 1.87 (0.4, 8.67)		P>0.05	Phet=0.39
		1 trial (fair quality) N=78				Intra-abdominal infection	RR (95% CI): 0.33 (0.04, 3.07)		P>0.05	P=NA
		1 trial (fair quality) N=130				Intra-abdominal collection requiring drainage	RR (95% CI): 1.26 (0.061, 2.60)		P>0.05	Phet=NA
		2 trials (fair quality) N=208				Wound infection	RR (95% CI): 0.84 (0.34, 2.03)		P>0.05	Phet=0.18
		1 trial (fair quality) N=78				Chest infection	RR (95% CI): 1.50 (0.27, 8.49)		P>0.05	Phet=NA

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Bennett (2006)	Level II *Fair*	N=155	Adults undergoing elective hip surgery.[2] Anticipated blood loss between 1 to 1.5 L.	Hospital in UK	Autologous blood was collected immediately before surgery, aiming to reduce Hb concentration to a target of 110 g per L. All autologous blood was returned within 6 hours of collection, starting on wound closure or sooner if a transfusion trigger was reached.	Patients with at least one significant postoperative complication.	14/78 (18%)	30/77 (38%)	P=0.006	
						Cardiovascular event	1/78 (1%)	4/77 (5%)	P=0.21	
						Postoperative infection	7/78 (9%)	17/77 (22%)	P=0.03	
						Wound (non-infective)	2/78 (3%)	0/77 (0%)	P=0.30	
						Bleeding	0/78 (0%)	1/77 (1%)	P=0.49	
						Venous thromboembolism	2/78 (3%)	1/77 (1%)	P=0.58	
						Urinary retention	3/78 (4%)	3/77 (4%)	P=0.99	
						Transfusion reaction	0/78 (0%)	1/77 (1%)	P=0.49	
Casati (2002)	Level II *Poor*	N=204	Adults undergoing cardiac surgery[3]	Hospital in Italy	Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions.	MI	2/103 (2%)	1/101 (1%)	P=0.58	
						Renal failure	3/103 (2.9%)	4/101 (4%)	P=0.68	
						Minor neurological complications	7/103 (6.9%)	8/101 (8%)	P=0.86	
						Stroke	2/103 (2%)	1/101 (1%)	P=0.58	
						Pulmonary embolism	0/103 (0%)	1/101 (1%)	P=0.49	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Casati (2004)	Level II *Fair*	N=100	Adults undergoing off-CPB CABG	Hospital in Italy	ANH with tranexamic acid (with tranexamic acid as control)	Respiratory failure	1/50 (2%)	1/50 (2%)	P=1.00	
						Atrial fibrillation	5/50 (10%)	6/50 (12%)	P=0.75	
						Major ventricular arrhythmia	1/50 (2%)	1/50 (2%)	P=1.00	
						Myocardial infarction	1/50 (2%)	1/50 (2%)	P=1.00	
						Creatinine double the baseline	1/50 (2%)	2/50 (4%)	P=0.57	
						Minor neurological complications	2/50 (4%)	1/50 (2%)	P=0.57	
Jarnagin (2008)	Level II *Fair*	N=130	Adults undergoing major hepatic resection (three or more liver segments) for any diagnosis, with or without any other planned procedures	Hospital in USA	ANH: blood was withdrawn to a target Hb concentration of 8.0 g/dL, with a maximum of 3 L of blood removed. Normovolemia was maintained by replacing half of the removed blood volume with 5% albumin and the other half with crystalloid.	Overall morbidity	28/63 (44%)	22/67 (33%)	P=0.17	
						Grade ≥ 3 morbidity	19/63 (30%)	19/67 (28%)	P=0.82	
Lim (2003)	Level II *Fair*	N=30	Adults undergoing spinal surgery	Hospital in South Korea	ANH and esmolol-induced controlled hypotension (E-ANH group): for ANH autologous blood was withdrawn from the radial artery aiming for 28% haematocrit. To maintain normovolemia, the first 500 mL of blood drawn was simultaneously replaced with an equal amount of 6% HES, and the blood thereafter was replaced with three times that volume of Lactated Ringer's solution.	General morbidity			All patients were evaluated 1 week after the operation, and there were no postoperative complications (thromboembolism, neurologic sequelae or wound infection) in either group.	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Matot (2002)	Level II *Fair*	N=78	Adults undergoing liver resection	Hospital in Israel	ANH: Preoperatively, blood was transfused into standard citrate-phosphate-dextrose blood storage bags, and was simultaneously replaced by colloid solutions. The volume of blood collected was 2,020 ± 412 mL.	Adverse cardiac, renal, or neurological outcomes	0/39 (0%)	0/39 (0%)	Not estimable	
Sanders (2004)	Level II *Fair*	N=160	Adults undergoing major gastrointestinal surgery (colorectal, gastric, or pancreatic)[4]	Hospital in UK	ANH: Maximum 3 units of blood withdrawn preoperatively and replaced with warmed cell-free fluid to maintain normovolemia. At the end of the operation, all autologous blood was re-transfused.	Pyrexia	0/78 (0%)	3/82 (4%)	P=0.21	
						UTI	8/78 (10%)	7/82 (9%)	P=0.71	
						RTI	2/78 (3%)	1/82 (1%)	P=0.54	
						Wound infection	3/78 (4%)	6/82 (7%)	P=0.35	
						Deep infection	1/78 (1%)	0/78 (0%)	P=0.48	
						Septicaemia	1/78 (1%)	1/82 (1%)	P=0.97	
						DVT	2/78 (3%)	2/82 (2%)	P=0.96	
						PE	0/78 (0%)	2/82 (2%)	P=0.31	
						Anastomotic leak	0/78 (0%)	3/82 (4%)	P=0.21	

Abbreviations: ANH, acute normovolemic haemodilution; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; Hb, haemoglobin; het, heterogeneity; NA, not applicable; NR, not reported; MI; myocardial infarction; PE, pulmonary embolism; RCT, randomised controlled trial; RR, relative risk; RTI, respiratory tract infection; UTI, urinary tract infection.

[1] Trials were included irrespective of whether they included major or minor liver resections, normal or cirrhotic livers, vascular occlusion was used or not, and irrespective of the reason for liver resection.

[2] Most patients underwent primary total hip replacement, with 15 revision hip arthroplasties (seven in ANH and eight in standard transfusion) and one hip resurfacing procedure.

[3] Procedures included single and multiple valve surgery, aortic root surgery, coronary surgery combined with valve surgery, or partial left ventriculectomy.

[4] These operations were considered high risk (>40%) for allogeneic transfusion

Key question(s): In patients undergoing surgery, what is the effect of ANH on quality of life?		Evidence table ref*: POQ3.I1.P6
1. Evidence base		
No evidence found	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on quality of life is unknown.

Abbreviations: ANH, acute normovolemic haemodilution; NA, not applicable.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of ANH on haemoglobin concentration?		Evidence table ref*: POQ3.I1.S1
1. Evidence base		
Level II evidence: 8 RCTs: Akhlagh 2007 (poor quality; N=60); Friesen 2006 (fair quality; N=32); Hohn 2002 (poor quality; N=80); Lim 2003 (fair quality; N=30); Matot 2002 (fair quality; N=78); Obasi 2006 (poor quality; N=62); Saricaoglu 2005 (good quality[1]; N=30); Wolowczyk 2003 (fair quality; N=36).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
With the exception of Wolowczyk 2003 and Obasi 2006, all of the studies are consistent in finding no significant association between ANH and haemoglobin concentration. Wolowczyk 2003 found that ANH was significantly associated with a lower median haemoglobin concentration at aortic clamping and clamp release but a significantly higher median haemoglobin concentration at 7 days postoperative. Obasi 2006 found significantly higher Hb concentration in the ANH group at 6-h post-surgery but not immediately post-surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
See evidence summary table POQ3.I1.S1 Evidence inconsistent	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered/inconsistent
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. The studies were conducted in adults undergoing cardiac, orthopaedic, liver and spinal surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Countries included Iran, USA, Switzerland, South Korea, Israel, Poland, Turkey, and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

There is a large variability in the reported timepoints and methods of analysis. The CRG considered outcomes at 7 days post operative most relevant. All the studies were underpowered. Intervention has a direct effect on Hb concentration so only trials that controlled would provide evidence.

The CRG considered that Obasi 2006 was not comparable because they did not report transfusion incidence or volume (ie, patients may not have been transfused).

Friesen 2006 was not taken into account as the study was in infants

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Several Level II studies with a moderate risk of bias
2. Consistency	C	Most studies consistent and inconsistency can be explained
3. Clinical impact	D	Underpowered/inconsistent
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on postoperative haemoglobin concentration is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; RCT, randomised control trial.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[1] Allocation to treatment groups was concealed from those responsible for recruiting subjects, patient characteristics and demographics were similar between treatment arms at baseline, all randomised patients were included in the analysis, the statistical methods were appropriate, and a transfusion protocol was reported. The study was not double-blinded.

POQ3.I1.S1 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on haemoglobin concentration.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Akhlagh (2007)	Level II *Poor*	N=60	Adults undergoing on-CPB CABG	Hospital in Iran	ANH and re-transfusion of autologous blood after separating the patient from the cardiopulmonary machine.	Mean (SD) haematocrit at 24 h postoperative, %	36.5 (1.5)	37 (2)	P=0.21	
Friesen (2006)	Level II *Fair*	N=32	Infants undergoing non-complex open cardiac surgery	Hospital in USA	ANH: 15 mL/kg whole blood withdrawn through the central venous catheter. Normovolemia was maintained by infusion of 1 mL of 5% albumin solution for each mL of blood withdrawn. Autologous blood re-transfused postoperatively.	Mean (SD) haematocrit at T1 (baseline), %	32 (3)	32 (4)	P=1.00	
						Mean (SD) haematocrit at T2 (following conclusion of CPB and modified ultrafiltration), %	32 (8)	34 (6)	P=0.42	
						Mean (SD) haematocrit at T3 (20 minutes after T2), %	33 (7)	34 (6)	P=0.66	
						Mean (SD) haematocrit at T4 (after 2 hours in the ICU), %	35 (8)	34 (5)	P=0.67	
						ΔT2 – T3, %	1 (2)	1 (1)	P=1.00	
						ΔT2 – T4, %	3 (4)	0 (3)	P=0.009	
Hohn (2002)	Level II *Poor*	N=80	Adults undergoing on-CPB cardiac surgery	Hospital in Switzerland	ANH from a mean haematocrit of 43% to 28%.	Mean (SD) haematocrit baseline, %	43.3 (3.9)	43.2 (2.4)	P=0.89	
						Mean (SD) haematocrit immediate postoperative, %	25 (3.5)	25.7 (3.3)	P=0.36	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Lim (2003)	Level II *Fair*	N=30	Adults undergoing spinal surgery	Hospital in South Korea	ANH and esmolol-induced controlled hypotension (E-ANH group): for ANH autologous blood was withdrawn from the radial artery aiming for 28% haematocrit. To maintain normovolemia, the first 500 mL of blood drawn was simultaneously replaced with an equal amount of 6% HES, and the blood thereafter was replaced with three times that volume of Lactated Ringer's solution.	Mean (SD) Hb one week postoperative, g/dL	11.3 (1.16)	11.3 (0.77)	P>0.05	
Matot (2002)	Level II *Fair*	N=78	Adults undergoing liver resection	Hospital in Israel	ANH: Preoperatively, blood was transfused into standard citrate-phosphate-dextrose blood storage bags, and was simultaneously replaced by colloid solutions. The volume of blood collected was 2,020 ± 412 mL.	Mean (SD) haematocrit (%) (before vs after)	40.8 ± 2.7 vs 23.5 ± 1.2 (P<0.05)	41.6 ± 3.2 vs 40.9 ± 2.8 (P>0.05)		
Obasi (2006)	Level II *Poor*	N=62	Adults undergoing surgical procedures	Hospital in Poland	Before the administration of anaesthesia, 500 to 800 mL of blood was effused from the patients (depending on body weight, values of Hb and haematocrit) with the simultaneous infusion of 6% HES in the ratio of 1:1 in an aseptic and closed circuit.	Mean (SD) Hb preoperative, mmol/L	8.37 (0.43)	8.37 (0.63)	P=1.00	
						Mean (SD) Hb immediately postoperative, mmol/L	6.45 (0.52)	6.46 (0.56)	P=0.94	
						Mean (SD) Hb 6 hours postoperative, mmol/L	7.20 (0.53)	6.48 (0.56)	P<0.00001	
Saricaoglu (2005)	Level II *Good*	N=30	Adults undergoing hip arthroplasty	Hospital in Turkey	ANH: autologous blood 15 mL/kg was withdrawn and replaced by ~15 mL/kg 6% HES HHD: 15 mL/kg HES administered without removal of any autologous blood	Median (95% CI) haematocrit preoperative, %	39.2 (34.6, 46.0)	HHD: 41.1 (37, 45.3) Control: 43.2 (35.8, 45.8)	P=0.5	
						Median (95% CI) haematocrit postoperative , %	32.7 (26.5, 38.6)	HHD: 29.1 (26.5, 38.6) Control: 32.3 (26.5, 38.6)	P=0.398	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
					Control: no haemodilution	Median (95% CI) haematocrit 24 h postoperative, %	32.7 (30.1, 40.1)	HHD: 34.9 (30.2, 36.7) Control: 32.9 (30, 36.5)	P=0.89	
Wolowczyk (2003)	Level II *Fair*	N=36	Adults undergoing abdominal aortic aneurysm repair	Hospital in UK	ANH and cell salvage: 15 g/kg of blood was withdrawn and replaced with a similar volume of 6% HES Control: standard care (including cell salvage)	Median (range) Hb preoperative, g/dL	14.2 (12.1 to 16.5)	13.8 (12.1 to 15.6)	P=0.57	
						Median (range) Hb post-ANH, g/dL	9.4 (7.0 to 12.1)	NA	NA	
						Median (range) Hb at aortic clamping, g/dL	9.2 (6.8 to 10.6)	11.3 (7.2 to 14.5)	P=0.001	
						Median (range) Hb at clamp release, g/dL	7.7 (6.6 to 9.3)	9.1 (5.1 to 11.9)	P=0.004	
						Median (range) Hb at 1-2 hours postoperative, g/dL	10.8 (8.8 to 13.3)	10.3 (8.1 to 12.7)	P=0.68	
						Median (range) Hb at 1 day postoperative, g/dL	10.4 (8.3 to 12.4)	10.4 (8.2 to 12.8)	P=0.68	
						Median (range) Hb at 2 days postoperative, g/dL	10.6 (8.2 to 13.3)	9.7 (8.5 to 13.7)	P=0.60	
						Median (range) Hb at 7 days postoperative, g/dL	11.5 (10.2 to 12.4)	10.7 (9.1 to 11.9)	P=0.021	

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; Hb, haemoglobin; HES, hydroxyethyl starch; HHD, hypervolemic haemodilution; NA, not applicable; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of ANH on reoperation for bleeding?		Evidence table ref*: POQ3.I1.S2
1. Evidence base		
Level I evidence: Carless 2004 (fair quality[1]; 7 trials, N=NR; adults undergoing any type of surgery) Level II evidence: Hohn 2002 (poor quality; N=80)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All studies are consistent in finding no significant impact. The studies were underpowered to find a significant difference.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Results from Carless 2004: RR 1.59 (0.20, 12.53); 7 trials; N=NR Results from Hohn 2002: RR 7.35 (0.39, 137.84)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Quality of RCTs in Carless 2004 not reported.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One Level I study and one Level II study with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	No difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on risk of reoperation for bleeding is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; NR, not reported; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] No quality assessment of included studies were undertaken, the characteristics of the individual studies were appropriately summarised, the sources of heterogeneity were not sufficiently explored.

POQ3.I1.S2 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on reoperation for bleeding.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2004)	Level I *Fair*	7 trials (quality NR) N=NR	Adults undergoing any type of surgery	All studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH	Proportion of patients who underwent reoperation for bleeding	RR (95% CI):1.59 (0.20, 12.53)		P>0.05	*Phet*=NR
Hohn (2002)	Level II *Poor*	N=80	Adults undergoing on-CPB cardiac surgery	Hospital in Switzerland	ANH from a mean haematocrit of 43% to 28%.	Proportion of patients who underwent reoperation for bleeding	3/39 (8%)	0/41 (0%)	P=0.18	

Abbreviations: ANH, acute normovolemic haemodilution; CI, confidence interval; CPB, cardiopulmonary bypass; het, heterogeneity; NR, not reported; RR, relative risk.

Key question(s): In patients undergoing surgery, what is the effect of ANH on correction/prevention of DIC and coagulopathy?		Evidence table ref*: POQ3.I1.S3
1. Evidence base		
Level II evidence: Saricaoglu 2005 (good quality[1]; N=30; adults undergoing hip arthroplasty). Friesen 2006 was not taken into account as the study was in infants. (fair quality; N=32; infants undergoing non-complex open cardiac surgery)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The two trials do not report the same coagulopathy outcomes; therefore the results are non-comparable.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
See evidence summary table POQ3.I1.S3	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
Saricaoglu 2005 was in adults undergoing hip arthroplasty.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Saricaoglu 2005 was conducted in Turkey.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Friesen 2006 was not taken into account as the study was in infants.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level II studies with moderate risk of bias
2. Consistency	NA	The two trials do not report the same coagulopathy outcomes; therefore the results are non-comparable
3. Clinical impact	D	Slight/Restricted clinical impact
4. Generalisability	C	Evidence is not directly generalisable to target population. One trial included 30 adult patients
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on coagulation parameters is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; DIC, disseminated intravascular coagulation.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] Allocation to treatment groups was concealed from those responsible for recruiting subjects, patient characteristics and demographics were similar between treatment arms at baseline, all randomised patients were included in the analysis, the statistical methods were appropriate, and a transfusion protocol was reported. The study was not double-blinded.

POQ3.I1.S3 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on correction/prevention of DIC and coagulopathy.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Friesen (2006)	Level II *Fair*	N=32	Infants undergoing non-complex open cardiac surgery	Hospital in USA	ANH: 15 mL/kg whole blood withdrawn through the central venous catheter. Normovolemia was maintained by infusion of 1 mL of 5% albumin solution for each mL of blood withdrawn. Autologous blood re-transfused postoperatively.	Mean (SD) platelet count at T1 (baseline), 10^9/L	353 (92)	335 (92)	P=0.58
						Mean (SD) platelet count at T2 (following conclusion of CPB and modified ultrafiltration), 10^9/L	126 (49)	140 (47)	P=0.42
						Mean (SD) platelet count at T3 (20 minutes after T2), 10^9/L	161 (55)	158 (57)	P=0.88
						Mean (SD) platelet count at T4 (after 2 hours in the ICU), 10^9/L	207 (53)	217 (59)	P=0.62
						Mean (SD) platelet count, ΔT2 – T3 (platelet count), 10^9/L	36 (22)	18 (17)	P=0.018
						Mean (SD) platelet count, ΔT2 – T4, 10^9/L	82 (43)	70 (42)	P=0.43
						Mean (SD) platelet aggregation at T1 (baseline), seconds	205 (62)	189 (54)	P=0.44
						Mean (SD) platelet aggregation at T2 (following conclusion of CPB and modified ultrafiltration), seconds	222 (71)	210 (70)	P=0.63
						Mean (SD) platelet aggregation at T3 (20 minutes after T2), seconds	144 (58)	159 (72)	P=0.52
						Mean (SD) platelet aggregation at T4 (after 2 hours in the ICU), seconds	112 (23)	113 (32)	P=0.92
						Mean (SD) platelet aggregation, ΔT2 – T3 (platelet count), seconds	-78 (53)	-49 (77)	P=0.22
						Mean (SD) platelet aggregation, ΔT2 – T4, seconds	-109 (67)	-97 (64)	P=0.61
						Mean (SD) prothrombin time at T1 (baseline), seconds	13.4 (0.9)	14.1 (1.1)	P=0.058
						Mean (SD) prothrombin time at T2 (following conclusion of CPB and modified ultrafiltration), seconds	20.4 (4.3)	19.9 (3.8)	P=0.73
						Mean (SD) prothrombin time at T3 (20 minutes after T2), seconds	18.1 (3.1)	18.9 (3.6)	P=0.51
						Mean (SD) prothrombin time at T4 (after 2 hours in the ICU), seconds	15.9 (2.1)	16.8 (2.0)	P=0.22

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
						Mean (SD) prothrombin time, ΔT2 – T3 (platelet count), seconds	-2.3 (1.9)	-0.9 (1.2)	P=0.015
						Mean (SD) prothrombin time, ΔT2 – T4, seconds	-4.5 (3.2)	-3.0 (2.7)	P=0.16
						Mean (SD) aPTT at T1 (baseline), seconds	35.9 (9.3)	36.9 (8.7)	P=0.76
						Mean (SD) aPTT at T2 (following conclusion of CPB and modified ultrafiltration), seconds	46.7 (14.2)	44.1 (12.6)	P=0.59
						Mean (SD) aPTT at T3 (20 minutes after T2), seconds	42.2 (14.1)	43.7 (13.1)	P=0.76
						Mean (SD) aPTT at T4 (after 2 hours in the ICU), seconds	37.8 (13.2)	41.9 (17.2)	P=0.46
						Mean (SD) aPTT, ΔT2 – T3 (platelet count), seconds	-4.4 (7.7)	-0.4 (9.6)	P=0.20
						Mean (SD) aPTT, ΔT2 – T4, seconds	-8.9 (11.0)	-2.3 (16.7)	P=0.20
						Mean (SD) fibrinogen concentration at T1 (baseline), mg/dL	235 (63)	215 (55)	P=0.35
						Mean (SD) fibrinogen concentration at T2 (following conclusion of CPB and modified ultrafiltration), mg/dL	109 (37)	129 (38)	P=0.14
						Mean (SD) fibrinogen concentration at T3 (20 minutes after T2), mg/dL	132 (44)	128 (32)	P=0.77
						Mean (SD) fibrinogen concentration at T4 (after 2 hours in the ICU), mg/dL	152 (51)	146 (36)	P=0.70
						Mean (SD) fibrinogen concentration, ΔT2 – T3 (platelet count), seconds	14 (9)	-1 (16)	P=0.0027
						Mean (SD) fibrinogen concentration ΔT2 – T4, seconds	35 (18)	17 (20)	P=0.019
Saricaoglu (2005)	Level II *Good*	N=30	Adults undergoing hip arthroplasty	Hospital in Turkey	ANH: autologous blood 15 mL/kg was withdrawn and replaced by ~15mL/kg 6% HES HHD: 15 mL/kg HES administered without removal of any autologous blood Control: no haemodilution	Median (95% CI) preoperative platelet count, 1000/mm^3	280 (132, 367)	HHD: 286 (240, 387) Control: 285 (240, 387)	P=0.98
						Median (95% CI) postoperative platelet count, 1000/mm^3	258 (123, 354)	HHD: 204 (167, 300) Control: 241 (175, 310)	P=0.96

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
						Median (95% CI) 24 h postoperative platelet count, 1000/mm^3	283 (138, 356)	HHD: 195 (163, 300) Control: 283 (190, 356)	P=0.010 (HHD)
						Median (95% CI) preoperative INR	1.1 (0.92, 1.3)	HHD: 1.15 (0.95, 1.4) Control: 1.15 (0.92, 1.14)	P=0.6
						Median (95% CI) postoperative INR	1.2 (1.1, 2.3)	HHD: 1.4 (1.2, 1.5) Control: 1.35 (1.2, 1.5)	P=0.052
						Median (95% CI) 24 h postoperative INR	1.2 (1.1, 1.87)	HHD: 1.2 (1.1, 1.3) Control: 1.2 (1.1, 1.3)	P=0.68
						Median (95% CI) preoperative aPTT, seconds	27.6 (26.4, 35.9)	HHD: 28.5 (26.8, 32.1) Control: 27.6 (26.4, 32.1)	P=0.4
						Median (95% CI) postoperative aPTT, seconds	26.75 (23.8, 32.3)	HHD: 33.8 (30.1, 35.6) Control: 27.5 (24.7, 34.2)	P=0.01 P(ANH v HHD)<0.008
						Median (95% CI) 24 h postoperative aPTT, seconds	26.5 (24.7, 30.1)	HHD: 30.1 (24.7, 34.2) Control: 24.2 (24.2, 34.7)	P=0.182

Abbreviations: ANH, acute normovolemic haemodilution; aPTT, activated partial thromboplastin time; CI, confidence interval; CPB, cardiopulmonary bypass; HES, hydroxyethyl starch; HHD, hypervolemic haemodilution; ICU, intensive care unit; INR, international normalised ratio; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of ANH on hospital length of stay?		Evidence table ref*: POQ3.I1.S5
1. Evidence base		
Level I evidence: Carless 2004 (fair quality; 3 trials[1], N=96; adults undergoing any type of surgery) and Gurusamy 2009 (good quality; 1 trial, N=130; adults undergoing liver resection) Level II evidence: 6 RCTs: Bennett 2006 (fair quality; N=155); Casati 2002 (poor quality; N=204); Casati 2004 (fair quality; N=100); Hohn 2002 (poor quality; N=80); Jarnagin 2008 (fair quality; N=130); Sanders 2004 (fair quality; N=160)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All the studies except Bennett (2006) are consistent in finding no significant impact.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Results from Carless 2004: Mean difference (95% CI), days: 0.21 (-1.26, 1.68) Results from Gurusamy 2009: Mean difference (95% CI), days: 0.0 (-2.66, 2.66) Results from Bennett (2006): ANH vs. control; median (IQR), days: 7 (6, 9) vs. 8 (6, 11); P=0.03 Results from Level II studies – see evidence summary table POQ3.I1.P5	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. The studies were conducted in adults undergoing cardiac, orthopaedic, liver and other surgeries.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level I studies and several Level II studies with a low risk of bias
2. Consistency	C	All studies consistent
3. Clinical impact	D	No statistically significant impact
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on length of hospital stay is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; CI, confidence interval; RCT, randomised controlled trial.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] Fair to poor quality.

POQ3.I1.S5 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on hospital length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2004)	Level I *Fair*	3 trials (quality NR) N=96	Adults undergoing any type of surgery	All studies conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	ANH	Mean difference (95% CI) hospital length of stay, days	0.21 (-1.26, 1.68)		P>0.05	Phet=NR
Gurusamy (2009)	Level I *Good*	1 trial (fair quality) N=130	Patients undergoing liver resection[1]	Studies conducted in USA, Israel, and China.	ANH	Mean difference (95% CI) length of hospital stay, days	0.0 (-2.66, 2.66)		P>0.05	Phet=NA
Bennett (2006)	Level II *Fair*	N=155	Adults undergoing elective hip surgery.[2] Anticipated blood loss between 1 to 1.5 L	Hospital in UK	Autologous blood was collected immediately before surgery, aiming to reduce haemoglobin concentration to a target of 110 g per L. All autologous blood was returned within 6 hours of collection, starting on wound closure or sooner if a transfusion trigger was reached.	Median (IQR) length of hospital stay, days	7 (6, 9)	8 (6,11)	P=0.03	
Casati (2002)	Level II *Poor*	N=204	Adults undergoing cardiac surgery[3]	Hospital in Italy	Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions.	Median (IQR) postoperative hospital stay, days	7 (6, 9)	7 (6, 8.25)	P=0.54	
Casati (2004)	Level II *Fair*	N=100	Adults undergoing off-CPB CABG	Hospital in Italy	ANH with tranexamic acid (with tranexamic acid as control)	Mean (IQR) postoperative hospital stay, days	6 (6, 7)	6 (6, 7)	NR	
Hohn (2002)	Level II *Poor*	N=80	Adults undergoing on-CPB cardiac surgery	Hospital in Switzerland	ANH from a mean haematocrit of 43% to 28%.	Mean (SD) postoperative length of hospital stay, days	13.1 (3.7)	13.4 (8.3)	P=0.83	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Jarnagin (2008)	Level II *Fair*	N=130	Adults undergoing major hepatic resection (three or more liver segments) for any diagnosis, with or without any other planned procedures	Hospital in USA	ANH: blood was withdrawn to a target Hb concentration of 8.0 g/dL, with a maximum of 3 L of blood removed. Normovolemia was maintained by replacing half of the removed blood volume with 5% albumin and the other half with crystalloid.	Median (range) length of hospital stay, days	7 (5 to 50)	7 (4 to 26)	P=0.33	
Sanders (2004)	Level II *Fair*	N=160	Adults undergoing major gastrointestinal surgery (colorectal, gastric, or pancreatic)[4]	Hospital in UK	Maximum 3 units of blood withdrawn and transfused into blood bags containing citrate-phosphate-dextrose (anticoagulant). Warmed cell-free fluid was administered during blood withdrawal to maintain normovolemia. At the end of the operation, all autologous blood was re-transfused.	Median (range) length of hospital stay, days	8 (5 to 110)	10 (5 to 92)	NS	

Abbreviations: ANH, acute normovolemic haemodilution; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; IHb, haemoglobin; het, heterogeneity; NA, not applicable; NR, not reported; NS, not significant; QR, interquartile range; RCT, randomised controlled trial; SD, standard deviation.

[1] Trials were included irrespective of whether they included major or minor liver resections, normal or cirrhotic livers, vascular occlusion was used or not, and irrespective of the reason for liver resection.

[2] Most patients underwent primary total hip replacement, with 15 revision hip arthroplasties (seven in ANH and eight in standard transfusion) and one hip resurfacing procedure.

[3] Procedures included single and multiple valve surgery, aortic root surgery, coronary surgery combined with valve surgery, or partial left ventriculectomy.

[4] These operations were considered high risk (>40%) for allogeneic transfusion.

Key question(s): In patients undergoing surgery, what is the effect of ANH on ICU admission and length of stay?		Evidence table ref*: POQ3.I1.S6
1. Evidence base		
Level II evidence: 3 RCTs: Casati 2002(poor quality; N=204); Casati 2004 (fair quality; N=100); Hohn 2002 (poor quality; N=80)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All studies are consistent in finding no significant impact	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
ANH vs. control Casati 2002: Median (IQR) ICU stay, days: 1 (1, 1) vs. 1 (1, 2); P=0.49; N=204 Casati 2004: Mean (IQR) ICU stay, days: 1 (1, 1) vs. 1 (1, 1); P=1; N=100 Hohn 2002: Mean (SD) length of ICU stay, days: 3.1 (1.3) vs. 3.0 (1.3); P=0.73; N=80	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
All studies were in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The studies were conducted in Italy (Casati 2002 and 2004) and Switzerland (Hohn 2002)	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Three Level II studies with moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	No difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on length of ICU stay is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; ICU, intensive care unit; IQR, interquartile range; RCT, randomised controlled trial.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I1.S6 Characteristics and results of studies examining the effect of acute normovolemic haemodilution on ICU admission and length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Casati (2002)	Level II *Poor*	N=204	Adults undergoing cardiac surgery[1]	Hospital in Italy	Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions.	Median (IQR) ICU stay, days	1 (1, 1)	1 (1, 2)	P=0.49
Casati (2004)	Level II *Fair*	N=100	Adults undergoing off-CPB CABG	Hospital in Italy	ANH with tranexamic acid (with tranexamic acid as control)	Mean (IQR) ICU stay, days	1 (1, 1)	1 (1, 1)	P=1
Hohn (2002)	Level II *Poor*	N=80	Adults undergoing on-CPB cardiac surgery	Hospital in Switzerland	ANH from a mean haematocrit of 43% to 28%.	Mean (SD) length of ICU stay, days	3.1 (1.3)	3.0 (1.3)	P=0.73

Abbreviations: ANH, acute normovolemic haemodilution; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.
[1] Procedures included single and multiple valve surgery, aortic root surgery, coronary surgery combined with valve surgery, or partial left ventriculectomy.

Recommendation(s) for acute normovolemic haemodilution

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In adult patients undergoing surgery in which substantial blood loss is anticipated, the use of acute normovolemic haemodilution should be considered.	C	PO3.I1.P1, PO3.I1.P2

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Use of ANH will increase (not widely used at present).		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Training and equipment costs.		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Increased preoperative time; placement of bigger neck (jugular) lines; increased vascular complications (due to neck lines); theatre scheduling; extension of theatre utilisation time; requirement for a protocol.		
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Appropriate venesection equipment; blood bag requirements from Blood Bank.		
What could help to facilitate implementation of the recommendation?		
Development of a local ANH protocol.		

Intervention 2 – Intraoperative cell salvage

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on transfusion incidence?		Evidence table ref*: POQ3.I2.P1
1. Evidence base		
Pivotal evidence: 1 level I SR (Carless 2006): good quality; adults undergoing any type of surgery; all of the studies used a transfusion protocol; includes 5 RCTs (N=382): 2 vascular (1 fair and 1 poor quality), 2 cardiac (fair quality), 1 orthopaedic (fair quality) Supportive data published after Carless 2006 from 6 level II studies: Damgaard 2006 (cardiac; good quality; N=60); Goel 2007 (cardiac; fair quality; N=50); Mercer 2004 (vascular; good quality; N=81); Murphy 2005 (cardiac; fair quality; N=61); Wiefferink 2007 (cardiac; fair quality; N=30); Zhang 2004 (orthopaedic; poor quality; N=48)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The results are not consistent by surgery type (See meta-analysis in technical report). Within surgery types The two trials assessing cell salvage in orthopaedic surgery are consistent in reporting a significantly lower transfusion incidence in the cell salvage groups. There is inconsistency in the trials assessing cell salvage in cardiac and vascular surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Meta-analysis of systematic review and 4 of the RCTs (Goel 2007; Mercer 2004; Murphy 2005; Zhang 2004)[1]. Patients transfused with allogeneic blood. All surgery types – RR 0.61 (0.46, 0.81); 9 RCTs (N=621) Cardiac surgery – RR 0.63 (0.41, 0.98); 4 RCTs (N=316) Orthopaedic surgery – RR 0.33 (0.22, 0.49); 2 RCTs (N=88) Vascular surgery – RR 0.83 (0.67, 1.03); 3 RCTs (N=217)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Most of the studies were conducted in developed countries. Goel 2007 was conducted in India and Zhang was conducted in China.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Cardiac surgery included one good quality study; however, it couldn't be included in the meta-analysis because it reported transfusion of allogeneic blood components rather than allogeneic blood. Therefore this study was not taken into account when rating the evidence base for cardiac surgery.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One level I study and several level II studies with low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	There is a substantial clinical impact
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intraoperative cell salvage reduces the incidence of allogeneic blood transfusion.

Abbreviations: RCT, randomised controlled trial; RR, relative risk; SR, systematic review.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] Damgaard 2006 and Wiefferink 2007 were not included in the meta-analysis, because instead of measuring the incidence of allogeneic blood transfusion they measured transfusion of blood components and transfusion of packed RBCs respectively. See Summary Table I2.P1.

POQ3.I2.P1 Characteristics and results of studies examining the effect of intraoperative cell salvage on transfusion incidence.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I *Good*	5 trials (1 poor quality, 4 fair quality) N=382	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Allogeneic blood	74/191 (41%)	113/191 (59%)	P=0.03	Phet=0.01
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.	Allogeneic blood components	17/30 (57%)	21/29 (72%)	P=0.21	
Goel (2007)	Level II *Fair*	N=50	Adults undergoing off-pump coronary artery bypass grafting.	Hospital in India	Intraoperative cell salvage and autotransfusion of washed shed blood and transfusion of allogeneic blood if required.	Allogeneic blood	20/24 (83%)	25/25 (100%)	P=0.07	
Mercer (2004)	Level II *Good*	N=81	Adults undergoing surgery for abdominal aortic aneurysm.	Hospital in UK	Intraoperative cell salvage. Processed blood was returned to the patient as soon as haemostasis had been achieved.	Allogeneic blood	21/40 (53%)	31/41 (76%)	P=0.04	
Murphy (2005)	Level II *Fair*	N=61	Patients scheduled for non-emergency first-time CABG (off-pump)	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure.	Allogeneic blood components	5/30 (17%)	11/31 (36%)	P=0.11	
						Allogeneic blood	4/30 (13%)	7/31 (23%)	P=0.36	
						Platelets	2/30 (7%)	6/31 (19%)	P=0.17	
Wiefferink (2007)	Level II *Fair*	N=30	Adults undergoing CABG with CPB	Hospital in the Netherlands	Intraoperative cell salvage: The mediastinal and residual CPB blood was processed by a continuous autotransfusion system before reinfusion.	Allogeneic packed RBCs	8/15 (54%)	10/15 (67%)	P=0.46	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Zhang (2004)	Level II *Poor*	N=48	Adults undergoing operation for scoliosis.	Hospital in China	Intraoperative cell salvage and retransfusion of washed autologous blood.	Allogeneic blood	11/36 (31%)	12/12 (100%)	P<0.00001	
Cardiac surgery										
Carless (2006)	Level I *Good*	2 trials (fair quality) N=206	Adult patients undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Allogeneic blood	31/103 (30%)	56/103 (54%)	P=0.0009	Phet=0.32
Orthopaedic surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=40	Adult patients undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Allogeneic blood	6/20 (30%)	18/20 (90%)	P=0.002	Phet=NA
Vascular surgery										
Carless (2006)	Level I *Good*	2 trials (1 poor, 1 fair quality) N=136	Adult patients undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Allogeneic blood	37/68 (54%)	39/68 (57%)	P=0.58	Phet=0.58

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; NA, not applicable; RBC, red blood cells.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on transfusion volume?		Evidence table ref*: POQ3.I2.P2
1. Evidence base		
Pivotal evidence: 1 level 1 SR (Carless 2006); good quality; adults undergoing any type of surgery; includes 6 RCTs (N=432): 2 cardiac (fair quality), 1 orthopaedic (fair quality), 3 vascular (2 fair quality, 1 poor quality) Supportive published after Carless 2006 from 7 level II studies: Bowley 2006 (trauma; fair quality; N=44); Damgaard 2006 (cardiac; good quality; N=60); Goel 2007 (cardiac; fair quality; N=50); Mercer 2004 (vascular; good quality; N=81); Niranjan 2006 (cardiac; good quality; N=80); Selo-Ojeme 2007 (ruptured ectopic pregnancy; fair quality; N=112); Wiefferink 2007 (cardiac; fair quality; N=30)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The results are not consistent by surgery type. Within surgery types (of the RCTs included in the updated meta-analysis[1] conducted herein) The results are consistently significant in cardiac surgery (3 RCTs), and consistently insignificant in vascular surgery (3 RCTs) (see meta-analysis). Consistency with RCTs not included in the updated meta-analysis The results from Mercer 2004 are inconsistent with the results from the updated meta-analysis. Selo-Ojeme 2007 found that cell salvage in ruptured ectopic pregnancy significantly reduced the proportion of women requiring transfusion of > 1000 mL of blood. The results of the other RCTs agreed with those of the updated meta-analysis.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Meta-analysis of Carless 2006 and 2 RCTs (Goel 2007 and Bowley 2006) was conducted. All surgery types – mean difference -0.86 (-1.54, -0.18); 8 RCTs Cardiac surgery – mean difference -0.58 (-0.93, -0.23); 3 RCTs (N=256) Orthopaedic surgery – mean difference -2.04 (-2.58, -1.50); 1 RCT (N=40) Vascular surgery – mean difference 0.02 (-0.34, 0.38); 3 RCTs (N=186) Penetrating trauma– mean difference -4.70 (-8.01, -1.39); 1 RCT (N=44)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
Both elective (cardiac, orthopaedic, and vascular) surgery and surgery for traumatic injury are included in the review. The efficacy of intraoperative cell salvage is dependent on surgery type.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Most of the studies were conducted in developed countries. Goel 2007 was conducted in India; however, the exclusion of this study does not impact the results. Bowley 2006 (trauma) was conducted in Johannesburg.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats (cardiac, ortho, vascular)
	C	Evidence probably applicable to Australian healthcare context with some caveats (trauma)
	D	Evidence not applicable to Australian healthcare context

Other factors

Further studies required to strengthen evidence base. Selo-Ojeme 2007 was a Nigerian study in women with ruptured ectopic pregnancy and the CRG decided to not make a separate Evidence Statement based on this study.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	In each surgery subgroup (except trauma) there are several Level II studies with a moderate risk of bias. In trauma surgery there is one Level II study with a moderate risk of bias.
2. Consistency	C	In vascular and orthopaedic surgery all studies are consistent. In cardiac surgery most studies are consistent and inconsistency can be explained
3. Clinical impact	C	Intraoperative cell salvage substantially reduces mean transfusion volume in orthopaedic and traumatic surgeries, moderately reduces mean transfusion in cardiac surgery, and does not significantly reduce mean transfusion in vascular surgery.
4. Generalisability	B	Evidence directly generalisable to target population with some caveats. Surgery types assessed include cardiac, orthopaedic, vascular, and surgery for penetrating trauma.
5. Applicability	B	In cardiac, vascular, and orthopaedic surgery evidence is applicable to Australian healthcare context with few caveats. The one study assessing trauma was conducted in Johannesburg.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intraoperative cell salvage may reduce the volume of allogeneic blood transfused.

Abbreviations: RCT, randomised controlled trial; SR, systematic review.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1]The following RCTs uncovered by the systematic update of Carless 2006 provided insufficient detail to be included in the meta-analysis: Damgaard 2006, Mercer 2004, Niranjan 2006, Selo-Ojeme 2007, and Wiefferink 2007.

[2]Mercer 2004 found that intraoperative cell salvage significantly reduces the median volume of allogeneic blood transfused in patients undergoing surgery for abdominal aortic aneurysm; a finding that is inconsistent with the meta-analytical results that reveal no significant impact of intraoperative cell salvage on volume transfused in patients undergoing vascular surgery.

POQ3.I2.P2 Characteristics and results of studies examining the effect of intraoperative cell salvage on transfusion volume.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I *Good*	6 trials (1 poor quality, 5 fair quality) N=432	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Units of allogeneic blood transfused Mean difference (95% CI)	-0.69 (-1.47, 0.08)		P=0.08	Phet<0.0001
Bowley (2006)	Level II *Fair*	N=44	Adults with penetrating torso injury requiring a laparotomy and who had exhibited hypotension either pre-hospital or an arrival and in whom there was considered to be a significant loss.	Hospital in Johannesburg	Intraoperative blood salvage with transfusion of both allogeneic and washed autologous blood.	Units of allogeneic blood transfused Mean (SD)	6.47 (5.14)	11.17 (6.06)	P=0.005	
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.	Units of allogeneic blood components transfused Median (IQR)	1 (0 to 2)	2 (0 to 7)	P=0.06	
						Units of allogeneic packed RBCs transfused Median (IQR)	1 (0 to 2)	2 (0 to 5)	P=0.07	
						Units of FFP transfused (ICU) Median (IQR)	0 (0 to 0) Range: 0 to 4	0 (0,0) Range: 0 to 22	P=0.40	
						Units of FFP transfused (ward) Median (IQR)	0 (0 to 0) Range: 0 to 0	0 (0, 0) Range: 0 to 1	P=0.31	
						Units of platelets transfused Median (IQR)	0 (0 to 0) Range: 0 to 1	0 (0 to 0) Range: 0 to 1	P=NR	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Goel (2007)	Level II *Fair*	N=50	Adults undergoing off-pump coronary artery bypass grafting.	Hospital in India	Intraoperative cell salvage and autotransfusion of washed shed blood and transfusion of allogeneic blood if required.	Units of allogeneic blood transfused Mean (SD)	1.5 (1.1)	2.4 (1.3)	P=0.008	
Mercer (2004)	Level II *Good*	N=81	Adults undergoing surgery for abdominal aortic aneurysm.	Hospital in UK	Intraoperative cell salvage. Processed blood was returned to the patient as soon as haemostasis had been achieved.	Units of allogeneic blood transfused Median (IQR)	1 (0 to 3)	3 (1 to 5)	P=0.012	
Niranjan (2006)	Level II *Good*	N=80	Adults undergoing first-time, isolated CABG	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure.	Volume of allogeneic blood transfused, mL Mean (SD)	On-CPB: 179 (214) Off-CPB: 141 (183) Combined: 159 (196)	On-CPB: 230 (240) Off-CPB: 595 (438) Combined: 413 (394)	On-CPB: P=0.048 Off-CPB: P<0.0001 Combined: P=0.0003	
Selo-Ojeme (2007)	Level II *Fair*	N=112	Women undergoing surgery for ruptured ectopic pregnancy	Hospital in Nigeria	Intraoperative cell salvage with transfusion of filtered autologous blood.	Patients transfused with ≥ 1000 mL with blood	34/56 (60%)	11/56 (20%)	P=0.0001	
Wiefferink (2007)	Level II *Fair*	N=30	Adults undergoing CABG with CPB	Hospital in the Netherlands	Intraoperative cell salvage: The mediastinal and residual CPB blood was processed by a continuous autotransfusion system before reinfusion.	Patients transfused with ≥ 2 units of allogeneic packed RBCs	2/15 (13%)	7/15 (47%)	P=0.08	
Cardiac surgery										
Carless (2006)	Level I *Good*	2 trials (fair quality) N=206	Adult patients undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Allogeneic blood Mean difference (95% CI)	-0.46 (-0.86, -0.05)		P=0.03	Phet=0.58
Orthopaedic surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=40	Adult patients undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Allogeneic blood Mean difference (95% CI)	-2.04 (-2.58, -1.50)		P<0.00001	Phet=NA

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Vascular surgery										
Carless (2006)	Level I *Good*	3 trials (1 poor quality, 2 fair quality) N=186	Adult patients undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Allogeneic blood Mean difference (95% CI)	0.02 (-0.32, 0.52)		P=0.91	Phet=0.42

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; NR, not reported; RBCs, red blood cells; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on operative blood loss?		Evidence table ref*: POQ3.I2.P3
1. Evidence base		
Pivotal evidence: 1 level 1 SR (Carless 2006); good quality; adults undergoing any type of surgery; includes 6 RCTs (N=431): 2 cardiac (fair quality), 1 orthopaedic (fair quality), 3 vascular (2 fair quality, 1 poor quality). Supportive evidence published after Carless 2006 from 4 level II studies: Damgaard 2006 (cardiac; good quality; N=60); Mercer 2004 (vascular; good quality; N=81); Niranjan 2006 (cardiac; good quality; N=80); Zhang 2004 (orthopaedic; poor quality; N=48)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Orthopaedic Intervention was associated with a significant reduction in blood loss in the 1 study included in Carless (2006) but there was no significant difference in Zhang 2004. Other surgery The results from Niranjan 2006 for on-CPB CABG patients are inconsistent with the results from Carless 2006. The results from Mercer 2004 and the off-CPB CABG patients in the Niranjan 2006 trial are consistent with the finding from Carless 2006 in finding no significant impact of cell salvage on blood loss.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless (2006) All surgery types – mean difference -108.47 mL (-407.53, 190.58); 6 RCTs (N=431) Cardiac surgery – mean difference 27.17 mL (-102.74, 157.08); 2 RCTs (N=206) Orthopaedic surgery – mean difference -736.00 mL (-1054.00, -418.00); 1 RCT (N=39) Vascular surgery – mean difference 34.62 mL (-268.98, 338.21); 3 trials (N=186)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight
4. Generalisability		
The results are generalisable for patients undergoing elective surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Orthopaedic One study was in China and the other in Europe Other surgery All the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

There is heterogeneity in the blood loss measures. Intuitively, cell salvage will not be expected to be a determinant of blood loss.

Damgaard 2006 only reported net blood loss.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	Two level II studies with moderate risk of bias in orthopaedic surgery. Several level II studies with low risk of bias for other surgery types.
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	D	Moderate impact in orthopaedic surgery. No difference in other surgery
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats (one orthopaedic study conducted in China)

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on operative blood loss is uncertain.

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; RCT, randomised controlled trial; SR, systematic review.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] All the studies were of fair quality.

POQ3.I2.P3 Characteristics and results of studies examining the effect of intraoperative cell salvage on blood loss.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I *Good*	6 trials (1 poor quality, 5 fair quality) N=431	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Mean difference (95% CI), mL	-108.47 (-407.53, 190.58)		P=0.48	Phet=0.001
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.	Median net blood loss (IQR), mL	300 (193 to 403)	610 (450 to 928)	P<0.001	
Mercer (2004)	Level II *Good*	N=81	Adults undergoing surgery for abdominal aortic aneurysm.	Hospital in UK	Intraoperative cell salvage. Processed blood was returned to the patient as soon as haemostasis had been achieved.	Median (IQR) blood loss, mL	1950 (775 to 285)	1270 (775 to 2850)	P=0.140	
Niranjan (2006)	Level II *Good*	N=80	Adults undergoing first-time, isolated CABG	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure.	Mean (SD) blood loss, mL	On-CPB: 842 (276) Off-CPB: 869 (286)	On-CPB: 1023 (291) Off-CPB: 903 (315)	On-CPB: P=0.04 Off-CPB: P=0.72	
Zhang (2004)	Level II *Poor*	N=48	Adults undergoing operation for scoliosis.	Hospital in China	Intraoperative cell salvage and retransfusion of washed autologous blood.	Mean (SD) blood loss	NR	NR	P=NS	
Cardiac surgery										
Carless (2006)	Level I *Good*	2 trials (fair quality) N=206	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Mean difference (95% CI), mL	27.17 (-102.74, 157.08)		P=0.68	Phet=0.96
Orthopaedic surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=39	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Mean difference (95% CI), mL	-736.00 (-1054.00, -418.00)		P<0.00001	Phet=NA

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Vascular surgery										
Carless (2006)	Level I *Good*	3 trials (1 poor quality, 2 fair quality) N=186	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Mean difference (95% CI), mL	34.62 (-268.98, 338.21)		P=0.82	Phet=0.83

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; NR, not reported; NS, not significant; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on mortality?		Evidence table ref*: POQ3.I2.P4
1. Evidence base		
Pivotal evidence: 1 level 1 SR (Carless 2006); good quality; adults undergoing any type of surgery; includes 3 RCTs (N=186): all vascular (1 poor quality, 2 fair quality) Supportive published after Carless 2006 from 7 level II studies: Bowley 2006 (trauma; fair quality; N=44); Damgaard 2006 (cardiac; good quality; N=60); Goel 2007 (cardiac; fair quality; N=50); Mercer 2004 (vascular; good quality; N=81); Murphy 2005 (cardiac; fair quality; N=61); Selo-Ojeme 2007 (ruptured ectopic pregnancy; fair quality; N=112); Zhang 2004 (orthopaedic; poor quality; N=48)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All the studies are consistent in finding no significant association between intraoperative cell salvage mortality.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Meta-analysis of Carless 2006 and the 7 RCTs was conducted All surgery types – RR 1.01 (0.68, 1.50); 10 RCTs (N=641) Cardiac surgery – RR 0.20 (0.01, 4.00); 3 RCTs (N=170) Trauma surgery – RR 1.02 (0.67, 1.56); 1 RCT (N=29) Vascular surgery – RR 1.16 (0.33, 4.09); 4 RCTs (N=267)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
Both elective (cardiac, orthopaedic, and vascular) surgery and surgery for traumatic injury are included in the review. The lack of effect of intraoperative cell salvage on mortality is not dependent on surgery type.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Most of the studies were conducted in developed countries. Goel 2007 was conducted in India, Selo-Ojeme 2007 in Nigeria, and Zhang 2004 in China. The exclusion of these studies does not impact the results.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Included studies were underpowered to detect a mortality difference. The high rates of mortality in Bowley 2006 was due to the study population (patients undergoing surgery for penetrating torso injury)

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	Two good quality level II studies with a low risk of bias and several other level II studies with moderate risk of bias
2. Consistency	A	All studies consistent because studies are underpowered
3. Clinical impact	D	There is no statistically significant association between intraoperative cell salvage and mortality
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on mortality is uncertain.

Abbreviations: RCT, randomised controlled trial; RR, relative risk; SR, systematic review.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I2.P4 Characteristics and results of studies examining the effect of intraoperative cell salvage on mortality.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I *Good*	3 trials (1 poor quality, 2 fair quality) N=186	Adults undergoing any type of surgery.[1]	All studies were conducted in developed countries.	Intraoperative cell salvage		4/93 (4%)	4/93 (4%)	P=0.93	Phet=0.18
Bowley (2006)	Level II *Fair*	N=44	Adults with penetrating torso injury requiring a laparotomy and who had exhibited hypotension either pre-hospital or an arrival and in whom there was considered to be a significant loss.	Hospital in Johannesburg	Intraoperative blood salvage with transfusion of both allogeneic and washed autologous blood.		14/21 (67%)	15/23 (65%)	P=0.92	
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.		0/30 (0%)	2/30 (7%)	P=0.29	
Goel (2007)	Level II *Fair*	N=50	Adults undergoing off-pump coronary artery bypass grafting.	Hospital in India	Intraoperative cell salvage and autotransfusion of washed shed blood and transfusion of allogeneic blood if required.		0/24 (0%)	0/25 (0%)	Not estimable	
Mercer (2004)	Level II *Good*	N=81	Adults undergoing surgery for abdominal aortic aneurysm.	Hospital in UK	Intraoperative cell salvage. Processed blood was returned to the patient as soon as haemostasis had been achieved.		1/40 (3%)	1/41 (2%)	P=1.000	
Murphy (2005)	Level II *Fair*	N=61	Patients scheduled for non-emergency first-time CABG (off-pump)	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure.		0/30 (0%)	0/31 (0%)	Not estimable	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Selo-Ojeme (2007)	Level II *Fair*	N=112	Women undergoing surgery for ruptured ectopic pregnancy	Hospital in Nigeria	Intraoperative cell salvage with transfusion of filtered autologous blood.		0/56 (0%)	0/56 (0%)	Not estimable	
Zhang (2004)	Level II *Poor*	N=48	Adults undergoing operation for scoliosis.	Hospital in China	Intraoperative cell salvage and retransfusion of washed autologous blood.		0/36 (0%)	0/12 (0%)	Not estimable	

Abbreviations: CABG, coronary artery bypass graft; ICU, intensive care unit; RBCs, red blood cells.

[1] All in vascular surgery

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on morbidity?		Evidence table ref*: POQ3.I2.P5
1. Evidence base		
Pivotal evidence: 1 level 1 SR (Carless 2006); good quality. Infection, 2 trials (1 cardiac, 1 vascular, both fair quality; N=268); wound complication, 1 trial (vascular, fair quality; N=100); any thrombosis, 2 trials (1 orthopaedic, 1 vascular, both fair quality; N=139); stroke, 2 trials (1 cardiac, 1 vascular, both fair quality; N=268); non-fatal MI, 3 trials (2 in vascular, 1 poor and 1 fair quality; 1 in cardiac; N=304); DVT, 1 trial (orthopaedic, fair quality N=39) Supportive evidence published after Carless 2006 from 7 level II studies: Damgaard 2006 (cardiac; good quality; N=60); Goel 2007 (cardiac, fair quality; N=50); Mercer 2004 (vascular, good quality; N=81); Murphy 2004 (vascular, fair quality; N=61); Niranjan 2006 (vascular, good quality; N=80); Selo-Ojeme 2007 (ruptured ectopic pregnancy, fair quality; N=112); Zhang 2004 (orthopaedic, poor quality; N=48)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
There was no association between intraoperative cell salvage and any reported adverse events in either Carless 2006 or the subsequent 7 RCTs with the following exceptions: • In Mercer 2004 there was a significantly lower rate of infection and SIRS in the cell salvage group. • In Zhang 2004 there was a significantly lower rate of allergic reactions in the cell salvage group. Infection in vascular surgery Carless 2006 reported no significant difference (10% vs 20%; P>0.05; N=100). In Mercer 2004 cell salvage was associated with a significant reduction in infection (13% vs 34%; P=0.03; N=81)	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Infection (a meta–analysis was conducted combining the results from Carless 2006 with those from Selo-Ojeme 2007, Damgaard 2006, Goel 2007, Murphy 2005, and Mercer 2004) Vascular - RR 0.42 (0.21, 0.83); 2 trials (N=181); Cardiac – RR 1.40 (0.62, 3.13); 4 trials (N=338); Trauma – RR 0.75 (0.18, 3.20); 1 trial (N=112) SIRS (Mercer 2004; N=81) – RR 0.46 (0.24, 0.89) Allergic reaction (Zhang 2004; N=48) – RR 0.05 (0.00, 0.91)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The results are generalisable for elective, non-emergency surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Most of the studies were conducted in developed countries. Goel 2007 was conducted in India, Selo-Ojeme 2007 in Nigeria, and Zhang 2004 in China. The exclusion of these studies does not impact the results.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Zhang 2004 studies T-cell sets etc, and so was not considered relevant. The CRG noted that the definitions of infection in Mercer 2004 were not clear (and therefore it was not appropriate to make an evidence statement for this outcome).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One level I study and several level II studies with low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	D	Cell salvage is associated with a moderate reduction in the risk of infection. No statistically significant association was found between intraoperative cell salvage and other morbidity outcomes
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on morbidity is uncertain.

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; RCT, randomised controlled trial; RR, relative risk; SIRS, systemic inflammatory response syndrome; SR, systematic review.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I2.P5 Characteristics and results of studies examining the effect of intraoperative cell salvage on morbidity.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I *Good*	2 trials (fair quality) N=268	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Infection	16/134 (12%)	17/134 (13%)	P=0.86	Phet=0.09
		1 trial (fair quality) N=100				Wound complication	3/50 (6%)	3/50 (6%)	P=1.00	Phet=NA
		2 trials (fair quality) N=139				Any thrombosis	3/69 (4%)	2/70 (3%)	P=0.59	Phet=NA
		2 trials (fair quality) N=268				Stroke	1/134 (1%)	3/134 (2%)	P=0.39	Phet=0.84
		3 trials (1 poor, 2 fair quality) N=304				Non fatal MI	5/152 (3%)	13/152 (9%)	P=0.09	Phet=0.84
		1 trial (fair quality) N=39				DVT	3/19 (16%)	2/20 (10%)	P=0.59	Phet=NA
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.	Stroke	0/30 (0%)	1/30 (3%)	P=0.50	
						MI	0/30 (0%)	1/30 (3%)	P=0.50	
						Pneumonia	2/30 (7%)	3/30 (10%)	P=0.64	
						GI bleeding	0/30 (0%)	3/30 (10%)	P=0.19	
						Deep sterna wound infection	0/30 (0%)	1/30 (3%)	P=0.50	
						Leg wound infection	0/30 (0%)	1/30 (3%)	P=0.50	
						Dialysis	1/30 (3%)	2/30 (7%)	P=0.56	
						Low cardiac output syndrome	0/30 (0%)	6/30 (20%)	P=0.08	
						Atrial arrhythmia	14/30 (47%)	20/30 (67%)	P=0.13	
						Ventricular arrhythmia	0/30 (0%)	3/30 (10%)	P=0.19	
Goel (2007)	Level II *Fair*	N=50	Adults undergoing off-pump coronary artery bypass grafting.	Hospital in India	Intraoperative cell salvage and autotransfusion of washed shed blood and transfusion of allogeneic blood if required.	Deep sterna wound infection	0/24 (0%)	0/25 (0%)	Not estimable	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Mercer (2004)	Level II *Good*	N=81	Adults undergoing surgery for abdominal aortic aneurysm.	Hospital in UK	Intraoperative cell salvage. Processed blood was returned to the patient as soon as haemostasis had been achieved.	Infection	5/40 (13%)	14/41 (34%)	P=0.03	
						Sepsis	4/40 (10%)	8/41 (20%)	P=0.49	
						SIRS	9/40 (23%)	20/41 (49%)	P=0.02	
Murphy (2005)	Level II *Fair*	N=61	Patients scheduled for non-emergency first-time CABG (off-pump)	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure.	Stroke	0/30 (0%)	0/31 (0%)	Not estimable	
						MI	2/30 (7%)	0/31 (0%)	P=0.28	
						Pulmonary complications	0/30 (0%)	4/31 (13%)	P=0.11	
						Infection	2/30 (7%)	1/31 (3%)	P=0.54	
						Renal complications	0/30 (0%)	2/31 (7%)	P=0.49	
						Arrhythmia	6/30 (20%)	7/31 (23%)	P=0.81	
Niranjan (2006)	Level II *Good*	N=80	Adults undergoing first-time, isolated CABG	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure.	Cardiovascular accident	On-CPB: 0/20 (0%) Off-CPB: 1/20 (5%)	On-CPB: 1/20 (5%) Off-CPB: 0/20 (0%)	On-CPB: P=0.49 Off-CPB: P=0.49	
						pulmonary complications	On-CPB: 4/20 (20%) Off-CPB: 2/20 (10%)	On-CPB: 3/20 (15%) Off-CPB: 1/20 (5%)	On-CPB: P=0.68 Off-CPB: P=0.56	
						Renal complications	On-CPB: 2/20 (10%) Off-CPB: 1/20 (5%)	On-CPB: 1/20 (5%) Off-CPB: 0/20 (0%)	On-CPB: P=0.56 Off-CPB: P=0.49	
						Arrhythmia	On-CPB: 7/20 (35%) Off-CPB: 3/20 (25%)	On-CPB: 5/20 (25%) Off-CPB: 4/20 (20%)	On-CPB: P=0.49 Off-CPB: P=0.68	
Selo-Ojeme (2007)	Level II *Fair*	N=112	Women undergoing surgery for ruptured ectopic pregnancy	Hospital in Nigeria	Intraoperative cell salvage with transfusion of filtered autologous blood.	Infection	3/56 (5%)	4/56 (7%)	P=0.70	
						Postoperative fever	20/56 (36%)	21/56 (38%)	P=0.84	
Zhang (2004)	Level II *Poor*	N=48	Adults undergoing operation for scoliosis.	Hospital in China	Intraoperative cell salvage and retransfusion of washed autologous blood.	Allergic reaction	0/36 (0%)	3/12 (25%)	P=0.04	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Cardiac surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=168	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Infection	11/84 (13%)	7/84 (8%)	P=0.32	Phet=NA
		1 trial (fair quality) N=168				Non fatal MI	5/84 (6%)	10/84 (12%)	P=0.19	Phet=NA
Orthopaedic surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=39	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Any thrombosis	3/19 (16%)	2/20 (10%)	P=0.59	Phet=NA
		1 trial (fair quality) N=168				Stroke	1/84 (1%)	2/84 (2%)	P=0.57	Phet=NA
Vascular surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=100	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage	Infection	5/50 (10%)	10/50 (20%)	P=0.17	Phet=NA
		1 trial (fair quality) N=100				Wound complication	3/50 (6%)	3/50 (6%)	P=1.00	Phet=NA
		1 trial (fair quality) N=100				Any thrombosis	0/50 (0%)	0/50 (0%)	Not estimable	Phet=NA
		1 trial (fair quality) N=100				Stroke	0/50 (0%)	1/50 (2%)	P=0.50	Phet=NA
		2 trials (1 poor, 1 fair quality) N=136				Non fatal MI	0/68 (0%)	3/68 (4%)	P=0.22	Phet=0.84

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; DVT; deep vein thrombosis; GI, gastrointestinal; ICU, intensive care unit; NA, not applicable; MI, myocardial infarction; RBCs, red blood cells; SIRS; systemic inflammatory response syndrome.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on quality of life?		Evidence table ref*: POQ3.I2.P6
1. Evidence base		
No evidence found	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on quality of life is unknown.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on haemoglobin concentration?		Evidence table ref*: POQ3.I2.S1
1. Evidence base		
Five Level II studies: Damgaard 2006 (cardiac; good quality; N=60); Goel 2007 (cardiac; fair quality; N=50); Murphy 2005 (cardiac; fair quality; N=61); Niranjan 2006 (cardiac; good quality; N=80); Selo-Ojeme 2007 (ruptured ectopic pregnancy; fair quality; N=112) Murphy 2005 reports the postoperative Hb concentration but not the preoperative concentration. Goel 2007 and Niranjan 2006 report the change in Hb concentration from preoperative to postoperative. Damgaard 2006 reports preoperative and postoperative Hb concentration values. Murphy 2005 and Selo-Ojeme 2007 report the postoperative, but not the preoperative, concentration of haematocrit in the cell salvage and control groups. Damgaard 2006 reports both pre and postoperative haematocrit concentration values.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Haemoglobin concentration: Goel 2007 reported a lesser decrease in Hb from pre- to postoperative levels, for cell salvage compared with control but Niranjan 2006 found no significant difference. Murphy 2005 found that the cell salvage group had significantly higher Hb concentration at 24 hours postoperative compared with control. Damgaard 2006 found no significant difference in Hb concentration either pre- or postoperatively. Haematocrit concentration: Damgaard 2006 found no significant difference in haematocrit concentration between the cell salvage and control groups either pre- or postoperatively. Murphy 2005 and Selo-Ojeme 2007 found that the haematocrit concentration was significantly greater in the cell salvage group 24 hours postoperative and immediately postoperative respectively.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Goel 2007 (cell salvage vs. control; mean difference in the decrease in Hb concentration from preoperative to immediately postoperative; g/dL) – mean difference -0.90 (-1.68, -0.12). Niranjan 2006 (cell salvage vs. control; mean difference in the Hb concentration from preoperative to 24 hours postoperative; g/dL): On-CPB – mean difference 0.55 (-0.07, 1.17), Off-CPB – mean difference -0.05 (-1.01, 0.91). Damgaard 2006 found no significant difference in Hb concentration between the cell salvage and the control groups either pre- or postoperatively.[a] Murphy 2005 found that the cell salvage group had significantly higher Hb concentration at 24 hours postoperative compared with control.[b] See Summary Table POQ3.I2.S1 for haematocrit concentration results.[c]	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
Damgaard 2006, Goel 2007, and Murphy 2005 were conducted in patients undergoing off-CPB CABG. Niranjan 2006 was conducted in patients undergoing on- and off-CPB CABG. Selo-Ojeme 2007 was assessed cell salvage in women with ruptured ectopic pregnancy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population & hard to judge whether it is sensible to apply
5. Applicability		
Murphy 2005 and Niranjan 2006 were conducted in UK, Damgaard 2006 in Denmark, Goel 2007 in India, and Selo-Ojeme 2007 in Nigeria.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

The results were not able to be meta-analysed because of insufficient details in the reported data and differences in the measurement timing of haemoglobin concentration.

The CRG based their decision making on the results from Goel 2007 and Murphy 2005, which reported the most relevant timepoints.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	Five fair-to-good quality level II studies reported haemoglobin/haematocrit concentration as a clinical outcome, but only three level II studies (one fair, two good quality) reported both pre- and postoperative haemoglobin concentration values.
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question.
3. Clinical impact	D	Some of the trials found that intraoperative cell salvage had a moderate impact and some found no impact.
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence probably applicable to Australian healthcare context with some caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing off-pump coronary artery surgery, intraoperative cell salvage may increase postoperative haemoglobin concentration and haematocrit.

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; Hb, haemoglobin; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[a] Baseline mean difference not reported. See Summary Table P0Q3.I2.S1 for median [IQR] values and P-values.

[b] Results from Murphy 2005 (mean difference [g/dL]): immediately postoperative, -0.11 (-0.69, 0.47); 1 hour postoperative, 0.15 (-0.42, 0.72); 24 hours postoperative, 1.02 (0.45, 1.59).

[c] Results from Damgaard 2006: mean difference not reported, see Summary Table P0Q3.I2.S1 for median [IQR] values and P-values.
Results from Murphy 2005 (mean difference [g/dL]): immediately postoperative, 0.00 (-0.02, 0.02); 1 hour postoperative, 0.01 (-0.01, 0.02); 24 hours postoperative, 0.03 (0.01, 0.05).
Results from Selo-Ojeme: mean difference not reported, see Summary Table P0Q3.I2.S1 for median [IQR] values and P-values.

POQ3.I2.S1 Characteristics and results of studies examining the effect of intraoperative cell salvage on haemoglobin concentration.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.	Baseline Hb concentration (median [IQR]), mmol/L	7.9 (7.4 to 8.7)	8.2 (7.4 to 8.9)	P=0.43	
						Lowest Hb concentration in ICU (median [IQR]), mmol/L	5.9 (5.3 to 6.6)	5.8 (5.2 to 6.7)	P=0.97	
						Lowest Hb concentration in ward (median [IQR]), mmol/L	6.4 (5.9 to 6.8)	6.6 (5.8 to 7.1)	P=0.58	
						Lowest Hb concentration at hospital discharge (median [IQR]), mmol/L	7.1 (6.5 to 7.4)	7.2 (6.5 to 8.1)	P=0.25	
						Baseline haematocrit concentration (median [IQR]), %	39 (36 to 42)	41 (38 to 44)	P=0.21	
						Lowest haematocrit concentration in ICU (median [IQR]), mmol/L	29 (27 to 33)	29 (25 to 33)	P=0.69	
Goel (2007)	Level II *Fair*	N=50	Adults undergoing off-pump coronary artery bypass grafting.	Hospital in India	Intraoperative cell salvage and autotransfusion of washed shed blood and transfusion of allogeneic blood if required.	Decrease in Hb (from preoperative to immediately postoperative) (mean [SD]), g/dL	1.8 (1.2)	2.7 (1.6)	P=0.02	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Murphy (2005)	Level II *Fair*	N=61	Patients scheduled for non-emergency first-time CABG (off-pump)	Hospital in UK	Intraoperative cell salvage, with autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure.	Hb concentration immediately postoperative (mean [SD]), g/dL	11.14 (1.15)	11.25 (1.17)	P=0.71	
						Hb concentration 1 hour postoperative (mean [SD]), g/dL	10.55 (1.15)	10.40 (1.11)	P=0.60	
						Hb concentration 24 hours postoperative (mean [SD]), g/dL	11.71 (1.15)	10.69 (1.11)	P=0.0007	
						Haematocrit concentration immediately postoperative (mean [SD]), %	0.345 (0.033)	0.344 (0.033)	P=0.91	
						Haematocrit concentration 1 hour postoperative (mean [SD]), %	0.312 (0.033)	0.305 (0.033)	P=0.46	
						Haematocrit concentration 24 hour postoperative (mean [SD]), %	0.350 (0.033)	0.319 (0.033)	P=0.0008	
Niranjan (2006)	Level II *Good*	N=80	Adults undergoing first-time, isolated CABG	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure.	Decrease in Hb (from preoperative to 24 hours postoperative) (mean [SD]), g/dL	On-CPB: 4.95 (1.1) Off-CPB: 4.95 (1.5)	On-CPB: 4.4 (0.9) Off-CPB: 5.0 (1.6)	On-CPB: P=0.08 Off-CPB: P=0.92	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Selo-Ojeme (2007)	Level II *Fair*	N=112	Women undergoing surgery for ruptured ectopic pregnancy	Hospital in Nigeria	Intraoperative cell salvage with transfusion of filtered autologous blood.	Haematocrit concentration immediately postoperative, %	29	26	P<0.01	

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range; HB, haemoglobin; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on the rate of reoperation for bleeding?		Evidence table ref*: POQ3.I2.S2
1. Evidence base		
1 SR (Carless 2006); good quality; includes 2 RCTs (N=218): 1 cardiac (fair quality), 1 vascular (fair quality) 2 level II studies: Damgaard 2006 (cardiac; good quality; N=60); Goel 2007 (cardiac; fair quality; N=50)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All the studies are consistent in finding no significant association between intraoperative cell salvage and reoperation for bleeding.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless 2006 – RR 0.57 (0.12, 2.63) Damgaard 2006 – RR 0.33 (0.04, 3.03) Goel 2007 – No patients in either treatment arms required reoperation for bleeding. Meta-analysed results – RR 0.48 (0.13, 1.68)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
One of the trials in Carless 2006 was in cardiac surgery, and the other in vascular surgery. Damgaard 2006 assessed cell salvage in off-CPB CABG.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies in Carless 2006 were conducted in developed countries, Damgaard 2006 was conducted in Denmark, and Goel 2007 was conducted in India. The exclusion of Goel 2007 does not impact the results.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Included studies were underpowered to detect a difference in reoperation for bleeding.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One level I study including two RCTs and an additional two level II studies with moderate risk of bias published subsequently
2. Consistency	A	All studies consistent
3. Clinical impact	D	No difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats. Surgery types assessed are all cardiovascular.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on risk of reoperation for bleeding is uncertain.

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; RCT, randomised controlled trial; RR, relative risk; SR, systematic review.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I2.S2 Characteristics and results of studies examining the effect of intraoperative cell salvage on reoperation for bleeding.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I *Good*	2 trials (fair quality) N=218	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage		2/109 (2%)	4/109 (4%)	P=0.47	Phet=0.71
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.		1/30 (3%)	3/30 (10%)	P=0.35	
Goel (2007)	Level II *Fair*	N=50	Adults undergoing off-pump coronary artery bypass grafting.	Hospital in India	Intraoperative cell salvage and autotransfusion of washed shed blood and transfusion of allogeneic blood if required.		0/24 (0%)	0/25 (0%)	Not estimable	
Cardiac surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=168	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage		2/84 (2%)	3/84 (4%)	P=0.65	Phet=NA
Vascular surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=50	Adults undergoing any type of surgery.	All studies were conducted in developed countries.	Intraoperative cell salvage		0/25 (0%)	1/25 (4%)	P=0.49	Phet=NA

Abbreviations: ICU, intensive care unit; NA, not applicable.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on coagulation status?		Evidence table ref*: POQ3.I2.S3
1. Evidence base		
Two Level II studies: Murphy 2005 (cardiac; fair quality; N=61); Niranjan 2006 (cardiac; good quality; N=80) Murphy 2005 reports platelet count, prothrombin ratio, APTT, and fibrinogen concentration. Niranjan 2006 only reports prothrombin time	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The studies were consistent in finding no significant impact.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Neither of the studies found any significant difference between cell salvage and control for any of the coagulation parameters. See Summary Table POQ3.I2.S3	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
Both studies were conducted in patients undergoing first-time CABG.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Both studies were conducted in the UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

The reported platelet count in Murphy 2005 is not clinically significant. The reported standard deviations in Murphy 2005 may actually be standard errors.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	No difference
4. Generalisability	B	Both studies were in adults undergoing first-time CABG
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats (both studies conducted in UK)

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing off-pump coronary artery surgery, the effect of intraoperative cell salvage on coagulation status is uncertain.

Abbreviations: APTT, activated partial thromboplastin time; CABG, coronary artery bypass graft.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I2.S3 Characteristics and results of studies examining the effect of intraoperative cell salvage on coagulation status.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Murphy (2005)	Level II *Fair*	N=61	Patients scheduled for non-emergency first-time CABG (off-pump)	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure.	Platelet count 1 hour postoperative (mean [SD]), X109/L	192.8 (0.15)	189.7 (0.14)	NR	
						Platelet count 24 hour postoperative (mean [SD]), X109/L	225.4 (0.15)	218.2 (0.14)	NR	
						Prothrombin ratio immediately postoperative (mean [SD])	1.27 (0.07)	1.27 (0.07)	NR	
						Prothrombin ratio 1 hour postoperative (mean [SD])	1.19 (0.06)	1.19 (0.06)	NR	
						Prothrombin ratio 24 hour postoperative (mean [SD])	1.15 (0.07)	1.15 (0.07)	NR	
						APTT ratio immediately postoperative (mean [SD])	1.17 (0.13)	1.14 (0.12)	NR	
						APTT ratio 1 hour postoperative (mean [SD])	1.08 (0.12)	1.13 (0.12)	NR	
						APTT ratio 24 hours postoperative (mean [SD])	1.08 (0.12)	1.11 (0.12)	NR	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
						Fibrinogen concentration immediately postoperative (mean [SD]), g/L	2.59 (0.20)	2.68 (0.18)	NR	
						Fibrinogen concentration 1 hour postoperative (mean [SD]), g/L	2.21 (0.19)	2.34 (0.18)	NR	
						Fibrinogen concentration 24 hours postoperative (mean [SD]), g/L	4.92 (0.19)	5.04 (0.19)	NR	
Niranjan (2006)	Level II *Good*	N=80	Adults undergoing first-time, isolated CABG (on-and off-CBP)	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure.	Prothrombin time	NR	NR	NS	
						Partial thromboplastin time (ratio)	NR	NR	NS	

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; NR, not reported; NS, not significant; RBC, red blood cells; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on hospital length of stay?		Evidence table ref*: POQ3.I2.S5
1. Evidence base		
1 SR Careless (2006): good quality; includes 1 RCT (N=100): vascular (fair quality) 6 level II studies: Bowley 2006 (trauma; fair quality; N=44); Damgaard 2006 (cardiac; good quality; N=60); Mercer 2004 (vascular; good quality; N=81); Murphy 2005 (cardiac; fair quality; N=61); Niranjan 2006 (cardiac; good quality; N=80); Selo-Ojeme 2007 (ruptured ectopic pregnancy; fair quality; N=112)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All the studies are consistent in finding no significant association between intraoperative cell salvage and length of hospital stay.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless 2006 – mean difference -0.50 (-2.46, 1.46); 1 trial (N=100) Bowley 2006 – mean difference 1.10 (-3.71, 5.91), N=44 Niranjan 2006 – mean difference (on-CPB) -0.20 (-1.82, 1.42); mean difference (off-CPB) -0.20 (-1.56, 1.16) Selo-Ojeme 2007: Length of hospital stay > 7 days; RR 1.33 (0.49, 3.59)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
The studies were conducted in patients undergoing cardiovascular surgery, surgery for penetrating trauma, and surgery for ruptured ectopic pregnancy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Most of the studies were conducted in developed countries. Selo-Ojeme 2007 was conducted in Nigeria; however, the exclusion of this study does not impact the results.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Length of stay is uncertain because of the range of surgeries.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	Several level II studies with low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	No difference
4. Generalisability	B	Evidence directly generalisable to target population with some caveats. Included studies assessed cardiovascular surgery, and surgery for trauma, and surgery for ruptured ectopic pregnancy.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on length of hospital stay is uncertain.

Abbreviations: CPB, cardiopulmonary bypass; RCT, randomised controlled trial; RR, relative risk; SR, systematic review.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I2.S5 Characteristics and results of studies examining the effect of intraoperative cell salvage on hospital length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I *Good*	1 trial (fair quality) N=100	Adults undergoing any type of surgery.[1]	All studies were conducted in developed countries.	Intraoperative cell salvage	Mean (SD), days	12.2 (4.7)	12.7 (5.3)	P=0.62	
Bowley (2006)	Level II *Fair*	N=44	Adults with penetrating torso injury requiring a laparotomy and who had exhibited hypotension either pre-hospital or an arrival and in whom there was considered to be a significant loss.	Hospital in Johannesburg	Intraoperative blood salvage with transfusion of both allogeneic and washed autologous blood.	Mean (SD), days	15.7 (9.17)	14.6 (6.8)	P=0.65	
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.	Median (IQR)	7 (6 to 8)	7 (6 to 9)	P=NS	
Mercer (2004)	Level II *Good*	N=81	Adults undergoing surgery for abdominal aortic aneurysm.	Hospital in UK	Intraoperative cell salvage. Processed blood was returned to the patient as soon as haemostasis had been achieved.	Median (IQR)	12 (8 to 19)	13 (10 to 19)	P=0.385	
Murphy (2005)	Level II *Fair*	N=61	Patients scheduled for non-emergency first-time CABG (off-pump)	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure.	Median (IQR)	6.0 (5.0, 8.3)	6.0 (5.0, 8.0)	P=0.73	
Niranjan (2006)	Level II *Good*	N=80	Adults undergoing first-time, isolated CABG	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure.	Mean (SD), days	On-CPB: 8.1 (2) Off-CPB: 7.2 (2.3)	On-CPB: 8.3 (3.1) Off-CPB: 7.4 (2.1)	On-CPB: P=0.81 Off-CPB: P=0.77	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Selo-Ojeme (2007)	Level II *Fair*	N=112	Women undergoing surgery for ruptured ectopic pregnancy	Hospital in Nigeria	Intraoperative cell salvage with transfusion of filtered autologous blood.	Length of hospital stay > 7 days	8/56 (14%)	6/56 (11%)	P=0.57	

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range; RBC, red blood cells; SD, standard deviation.

[1] The study was conducted in patients undergoing vascular surgery.

Key question(s): In patients undergoing surgery, what is the effect of intraoperative cell salvage on ICU admission and length of stay?		Evidence table ref*: POQ3.I2.S6
1. Evidence base		
Evidence for ICU readmission – 1 level II RCT: Murphy 2005 (cardiac; fair quality; N=61) Evidence for length of ICU stay – 3 level II studies: Damgaard 2006 (cardiac; good quality; N=60); Murphy 2005 (cardiac; fair quality; N=61); Niranjan 2006 (cardiac; good quality; N=80)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Evidence for ICU readmission – Not applicable (one study only) Evidence for length of ICU stay – All the studies are consistent in finding no significant association between intraoperative cell salvage and length of ICU stay.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Evidence for ICU readmission Murphy 2005 – RR 0.33 (0.04, 3.03) Evidence for length of ICU stay Damgaard 2006 (length of ICU stay > 24 hours) – RR 0.17 (0.02, 1.30) Murphy 2005 (cell salvage vs. control; median [IQR] length of ICU stay, days): 1.0 (1.0, 1.0) vs. 1.0 (1.0, 1.0) Niranjan 2006 (length of ICU stay in days): mean difference (on-CPB) -0.10 (-0.35, 0.15); mean difference (off-CPB) 0.10 (-0.10, 0.30)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
All three studies were conducted in patients undergoing CABG.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Two of the studies were conducted in the UK and the other in Denmark.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	Three level II studies with fair to good quality, with low risk of bias.
2. Consistency	A	All studies consistent
3. Clinical impact	D	No difference/underpowered
4. Generalisability	B	All studies are in patients undergoing CABG
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. Studies conducted in UK and Denmark.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of intraoperative cell salvage on ICU admission and length of stay is uncertain.

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range; RR, relative risk; SR, systematic review.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I2.S6 Characteristics and results of studies examining the effect of intraoperative cell salvage on ICU admission and length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Damgaard (2006)	Level II *Good*	N=60	Adults undergoing sub-acute coronary bypass surgery without heart-lung machine.	Hospital in Denmark	The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU.	Length of ICU stay > 24 hours	1/30 (3%)	6/30 (21%)	P=0.09	
Murphy (2005)	Level II *Fair*	N=61	Patients scheduled for non-emergency first-time CABG (off-pump)	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure.	Median (IQR) length of ICU stay, days	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	P=0.50	
						Readmission to ICU	1/30 (3%)	1/31 (3%)	P=0.98	
Niranjan (2006)	Level II *Good*	N=80	Adults undergoing first-time, isolated CABG	Hospital in UK	Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure.	Mean (SD) length of ICU stay, days	On-CPB: 0.9 (0.4) Off-CPB: 1 (0.4)	On-CPB: 1 (0.4) Off-CPB: 0.9 (0.2)	On-CPB: P=0.43 Off-CPB: P=0.32	

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range; RBCs, red blood cells; SD, standard deviation.

Recommendation(s) for intraoperative cell salvage

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In adult patients undergoing surgery in which substantial blood loss is anticipated, intraoperative cell salvage is recommended.	C	PO3.I2.P1, PO3.I2.P2, PO3.I2.S1

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Use of intraoperative cell salvage will increase.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Significant costs relating to equipment, training, and staffing (technicians).		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Workforce issues; organisational structure implications (scheduling use of the device).		
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Initial capital investment; recurrent expenditure (but preservation of blood supply at ARCBS level, which results in cost-shifting from Commonwealth to State).		
What could help to facilitate implementation of the recommendation?	YES	NO
Development of local policies for intraoperative cell salvage; lobbying for funding of cell salvage device.		

Intervention 3 – Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on transfusion incidence?		Evidence table ref*: POQ3.I3.P1
1. Evidence base		
Two level II studies: McGill 2002 (cardiac; fair quality; N=254); Wong 2002 (vascular; fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Both studies reported allogeneic blood transfusion incidence. The studies agreed in direction. In McGill 2002, ANH and cell salvage was associated with a significant reduction in transfusion incidence. In Wong 2002 the association was not significant, however this may be due to study size. A meta-analysis of the two studies found that the heterogeneity was not significant (P=0.54; I^2=0%).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one cardiac study and one vascular surgery study)
3. Clinical impact		
McGill 2002 (ANH + cell salvage vs. control)[1] Patents transfused with any allogeneic blood product – RR 0.69 (0.49, 0.95) Patients transfused with allogeneic blood – RR 0.66 (0.46, 0.95) Patients transfused with FFP – RR 0.98 (0.48, 1.98) Patients transfused with platelets – RR 0.98 (0.51, 1.87) Patients transfused with allogeneic blood (Wong 2002) – RR 0.77 (0.55, 10.07) Meta-analysed value for transfusion of allogeneic blood – RR 0.72 (0.56, 0.91)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted/No difference
4. Generalisability		
McGill 2002 was conducted in patients undergoing cardiac surgery and Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Both studies were conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

The inconsistencies between McGill 2002 and Wong 2002 are likely to be due to the slightly different outcomes reported. McGill 2002 reported perioperative transfusion, and Wong 2002 reported intraoperative transfusion.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two fair quality level II studies – one in patients undergoing cardiac surgery and one in patients undergoing aortic surgery.
2. Consistency	B	Most studies consistent and inconsistency can be explained.
3. Clinical impact	B	Substantial clinical impact
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. Both studies were conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, a combination of ANH and intraoperative cell salvage may reduce the incidence of allogeneic blood transfusion.

Abbreviations: ANH, acute normovolemic haemodilution; FFP, fresh frozen plasma; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] See summary table POQ3.I3.P1 for values comparing ANH + cell salvage vs. cell salvage alone.

POQ3.I3.P1 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on transfusion incidence.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
McGill (2002)	Level II *Fair*	N=254	Adults undergoing cardiac surgery	UK hospital	ANH and intraoperative cell salvage compared with cell salvage alone or control	Patients transfused with any allogeneic blood product (n/N [%])	33/86 (38%)	Cell salvage 32/84 (38%) Control 47/84 (56%)	Cell salvage P=0.97 Control P=0.02	
						Patients transfused with allogeneic blood (n/N [%])	29/86 (34%)	Cell salvage: 26/84 (31%) Control: 43/84 (51%)	Cell salvage P=0.70 Control P=0.02	
						Patients transfused with FFP (n/N [%])	13/86 (15%)	Cell salvage: 14/84 (17%) Control: 13/84 (15%)	Cell salvage P=0.78 Control P=0.95	
						Patients transfused with platelets (n/N [%])	15/86 (17%)	Cell salvage: 11/84 (13%) Control: 15/84 (18%)	Cell salvage P=0.43 Control P=0.94	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.	Patients transfused with allogeneic blood during surgery (n/N [%])	32/74 (43%)	40/71 (56%)	P=0.12	

Abbreviations: ANH, acute normovolemic haemodilution; FFP, fresh frozen plasma.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on transfusion volume?		Evidence table ref*: POQ3.I3.P2
1. Evidence base		
Two level II studies: McGill 2002 (cardiac surgery; fair quality; N=254); Wong 2002 (aortic surgery; fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Both studies found that ANH + cell salvage significantly reduced allogeneic blood transfusion volume.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
McGill 2002 (ANH + cell salvage vs. control)[1] Units of allogeneic blood transfused – mean difference -0.44 (-0.86, -0.02); P=0.04 Units of FFP transfused – mean difference -0.06 (-0.42, 0.30); P=0.74 Units of platelets transfused – mean difference 0.02 (-0.20, 0.24); P=0.86 Wong 2002 Median (IQR) units of allogeneic blood transfused, ANH + cell salvage vs. control: 0 (0 to 2) vs. 2 (0 to 4); P=0.008	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
McGill 2002 was conducted in patients undergoing cardiac surgery and Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Both studies were conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two fair quality level II studies.
2. Consistency	A	The results from both studies are consistent.
3. Clinical impact	C	Moderate clinical impact.
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied. Both studies were conducted in patients undergoing cardiovascular surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. Both studies were conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, a combination of ANH and intraoperative cell salvage may reduce the volume of allogeneic blood transfusion.

Abbreviations: ANH, acute normovolemic haemodilution; FFP, fresh frozen plasma; IQR, interquartile range.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] See summary table POQ3.I3.P1 for values comparing ANH + cell salvage vs. cell salvage alone.

POQ3.I3.P2 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on transfusion volume.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
McGill (2002)	Level II *Fair*	N=254	Adults undergoing cardiac surgery	UK hospital	ANH and intraoperative cell salvage compared with cell salvage alone or control	Units of allogeneic blood transfused during surgery[1] (mean [SD])	0.63 (1.22)	cell salvage – 0.68 (1.55) control – 1.07 (1.56)	Cell salvage P=0.82 Control P=0.04	
						Units of FFP transfused (mean [SD])	0.43 (1.12)	Cell salvage: 0.57 (1.47) Control: 0.49 (1.25)	Cell salvage P=0.49 Control P=0.74	
						Units of platelets transfused (mean [SD])	0.31 (0.81)	Cell salvage: 0.20 (0.62) Control: 0.29 (0.67)	Cell salvage P=0.32 Control P=0.86	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	ANH and intraoperative cell salvage[2]	Median units of allogeneic blood transfused during surgery (median [IQR])	0 (0 to 2)	2 (0 to 4)	P=0.008	
						Total units of allogeneic blood transfused during surgery (aneurysm patients)[3]	102	201	NR	
						Median units of allogeneic blood transfused during surgery (for all occlusive disease patients)[4]	0 (0 to 2)	0 (0 to 2)	Mean difference: NR; P=0.87	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
						Total units of allogeneic blood transfused (occlusive disease patients)[4]	15	50	NR	

Abbreviations: ANH, acute normovolemic haemodilution; FFP, fresh frozen plasma; IQR, intensive care unit; NR, not reported; SD, standard deviation.

[1] Nine patients needed a markedly higher amount of transfused blood (≥3 units). These patients were returned to the operating theatre for re-exploration of the mediastinum. A surgical cause of bleeding was found in seven of these patients (three in the control group and two each in the cell salvage and combined treatment groups).

[2] Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.

[3]Two of the patients required a laparotomy (one for massive bleeding from the proximal aortic anastomosis, one for upper gastrointestinal haemorrhage).

[4]Three patients had intraoperative bleeding and a further five required reoperation for intra-abdominal bleeding.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on blood loss?		Evidence table ref*: POQ3.I3.P3
1. Evidence base		
One level II study: Wong 2002 (aortic surgery; fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Median [IQR] intraoperative blood loss (ANH + cell salvage vs. control), mL: 921 (661 to 1374) vs 1000 (688 to 1734); P=0.37	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Wong 2002 was conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One fair quality level II study with moderate risk of bias.
2. Consistency	NA	Not applicable (one study only).
3. Clinical impact	D	No difference.
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied. The study was conducted in patients undergoing aortic surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. The study was conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on blood loss is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; IQR, interquartile range.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I3.P3 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on blood loss.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	ANH and intraoperative cell salvage[1]	Intraoperative blood loss (median [IQR]), mL	921 (661 to 1374)	1000 (688 to 1734)	P=0.37	

Abbreviations: ANH, acute normovolemic haemodilution; IQR, interquartile range.

[1] Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on mortality?		Evidence table ref*: POQ3.I3.P4
1. Evidence base		
One level II study: Wong 2002 (fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
RR 1.13 (0.54, 2.36); P=0.91; N=145	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Wong 2002 was conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

The study was underpowered to show a significant difference in this outcome.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One fair quality level II study with moderate risk of bias.
2. Consistency	NA	Not applicable (one study only).
3. Clinical impact	D	No difference/underpowered.
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied. The study was conducted in patients undergoing aortic surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. The study was conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of perioperative ANH and intraoperative cell salvage on mortality is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I3.P4 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on mortality.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	ANH and intraoperative cell salvage[1]	Mortality (n/N [%])	13/74 (18%)	11/71 (15%)	P=0.91	

Abbreviations: ANH, acute normovolemic haemodilution.

[1] Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on morbidity?		Evidence table ref*: POQ3.I3.P5
1. Evidence base		
Two level II studies: McGill 2002 (cardiac surgery; fair quality; N=254); Wong 2002 (aortic surgery; fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The studies are consistent in finding no significant impact of ANH + cell salvage on morbidity.	A	All studies consistent in finding no difference
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
McGill 2002 found no significant difference between ANH + cell salvage and control for the following morbidity outcomes: all perioperative complications; haemorrhagic complications; cerebrovascular accident; arrhythmias; renal failure; infection; or MI. McGill 2002 found no significant difference in adverse events between ANH + cell salvage and cell salvage alone. Wong 2002 found no significant difference between ANH + cell salvage and control for infection, minor transfusion reaction, cardiac events, and haemorrhagic complications. See Summary Table POQ.13.P5 for more details.	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
McGill 2002 was conducted in patients undergoing cardiac surgery and Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Both studies were conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

The studies were underpowered to show a significant difference in morbidity outcomes.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account

Component	Rating	Description
1. Evidence base	C	Two fair quality level II studies.
2. Consistency	A	Both studies are consistent.
3. Clinical impact	D	No difference/underpowered
4. Generalisability	C	Both studies were conducted in patients undergoing cardiovascular surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. Both studies were conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of perioperative ANH and intraoperative cell salvage on morbidity is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; MI, myocardial infarction.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I3.P5 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on morbidity.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
McGill (2002)	Level II *Fair*	N=254	Adults undergoing cardiac surgery	UK hospital	ANH and intraoperative cell salvage compared with cell salvage alone or control	All perioperative complications (n/N [%])	46/86 (53%)	Cell salvage: 46/84 (55%) Control: 42/84 (50%)	Cell salvage P=0.87 Control P=0.65	
						Haemorrhagic complications (n/N [%])	2/86 (2%)	Cell salvage: 2/84 (2%) Control: 3/84 (4%)	Cell salvage P=0.98 Control P=0.63	
						Cerebrovascular accident (n/N [%])	1/86 (1%)	Cell salvage: 1/84 (1%) Control: 2/84 (2%)	Cell salvage P=0.99 Control P=0.56	
						Arrhythmias (n/N [%])	20/86 (23%)	Cell salvage: 17/84 (20%) Control: 27/84 (32%)	Cell salvage P=0.63 Control P=0.20	
						Renal failure (n/N [%])	2/86 (2%)	Cell salvage: 1/84 (1%) Control: 0/84 (0%)	Cell salvage P=0.58 Control P=0.30	
						Infection (n/N [%])	7/86 (8%)	Cell salvage: 11/84 (13%) Control: 7/84 (8%)	Cell salvage P=0.30 Control P=0.96	
						MI (n/N [%])	4/84 (5%)	Cell salvage: 5/84 (6%) Control: 10/84 (12%)	Cell salvage P=0.97 Control P=0.17	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	ANH and intraoperative cell salvage*	Infection (n/N [%])	16/74 (22%)	19/71 (27%)	P=0.6	
						Minor transfusion reaction (n/N [%])	0/74 (0%)	1/71 (1%)	P=0.48	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
						Cardiac events (n/N [%])	13/74 (18%)	8/71 (11%)	P=0.4	
						Haemorrhagic complications (n/N [%])	5/74 (7%)	8/71 (11%)	P=0.35	

Abbreviations: ANH, acute normovolemic haemodilution; MI, myocardial infarction.

* Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on quality of life?		Evidence table ref*: POQ3.I3.P6
1. Evidence base		
No evidence found	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on quality of life is unknown.

Abbreviations: ANH, acute normovolemic haemodilution.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on change in haemoglobin		Evidence table ref*: POQ3.I3.S1
1. Evidence base		
One level II study: McGill 2002 (fair quality; N=254)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Median (IQR) haemoglobin concentration; ANH + cell salvage vs. control[1] Preoperative: 145 (138 to 150) vs. 142 (135 to 150); P=NR At admission to ICU: 108 (99 to 116) vs. 100 (91 to 107); P=NR 24 hours after surgery: 105 (96 to 113) vs. 100 (94 to 109); P=NR Three days after surgery: 108 (100 to 119) vs. 106 (98 to 112); P=NR	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
McGill 2002 was conducted in patients undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
McGill 2002 was conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

24 hours post-op was considered by the CRG to be most relevant.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One fair quality level II study with moderate risk of bias.
2. Consistency	NA	Not applicable (one study only).
3. Clinical impact	D	No significant impact.
4. Generalisability	C	The study was conducted in patients undergoing cardiac surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. The study was conducted in the UK

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on postoperative haemoglobin concentration is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; ICU, intensive care unit; IQR, interquartile range; NR, not reported.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[1] See summary table POQ3.I3.P1 for values comparing ANH + cell salvage vs. cell salvage alone.

POQ3.I3.S1 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on change in haemoglobin concentration.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
McGill (2002)	Level II *Fair*	N=254	Adults undergoing cardiac surgery	UK hospital	ANH and intraoperative cell salvage compared with cell salvage alone or control	Preoperative Hb concentration (median [IQR]), g/dL	145 (138 to 150)	Cell salvage: 145 (136 to 150) Control: 142 (135 to 150)	NR	
						Hb concentration on admission to ICU (median [IQR]), g/dL	108 (99 to 116)	Cell salvage: 105 (98 to 116) Control: 100 (91 to 107)	NR	
						Hb concentration 24 hours after surgery (median [IQR]), g/dL	105 (96 to 113)	Cell salvage: 104 (95 to 115) Control: 100 (94 to 109)	NR	
						Hb concentration 3 days after surgery (median [IQR]), g/dL	108 (100 to 119)	Cell salvage: 105 (98 to 115) Control: 106 (98 to 112)	NR	

Abbreviations: ANH, acute normovolemic haemodilution; Hb, haemodilution; ICU, intensive care unit; IQR, interquartile range; NR, not reported.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on reoperation for bleeding?		Evidence table ref*: POQ3.I3.S2
1. Evidence base		
One level II study: Wong 2002 (fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
RR 1.37 (0.55, 3.40); P=0.50	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Wong 2002 was conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One fair quality level II study with moderate risk of bias.
2. Consistency	NA	Not applicable (one study only).
3. Clinical impact	D	No difference/underpowered
4. Generalisability	C	The study was conducted in patients undergoing aortic surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. The study was conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on risk of reoperation for bleeding is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; RR, relative risk.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I3.S2 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on reoperation for bleeding.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	ANH and intraoperative cell salvage[1]	Reoperation (n/N [%])	10/74 (14%)	7/71 (10%)	P=0.50	

Abbreviations: ANH, acute normovolemic haemodilution.

[1] Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on length of hospital stay?		Evidence table ref*: POQ3.I3.S5
1. Evidence base		
Two level II studies: McGill 2002 (fair quality; N=254); Wong 2002 (fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Both studies are consistent in finding no significant difference between treatment arms.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
McGill 2002 (median [IQR]) Length of hospital stay (ANH + cell salvage vs. control): 170 (147.1 to 221.6) vs. 168.9 (140.3 to 219.3); P=NR Length of hospital stay (ANH + cell salvage vs. cell salvage alone): 170 (147.1 to 221.6) vs. 160.7 (145.5 to 198.8); P=NR Kruskal-Wallis P-value=0.724 Wong (2002) (median [IQR], ANH +cell salvage vs. control) Length of hospital stay: 10 (8 to 13) vs. 9 (7 to 12); P=0.17	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
McGill 2002 was conducted in patients undergoing cardiac surgery and Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Both studies were conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two fair quality level II studies, with a moderate risk of bias.
2. Consistency	A	Both studies consistent.
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied. Both studies were conducted in patients undergoing cardiac surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. Both studies were conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on hospital length of stay is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; IQR, interquartile range.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I3.S5 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on hospital length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
McGill (2002)	Level II *Fair*	N=254	Adults undergoing cardiac surgery	UK hospital	ANH and intraoperative cell salvage compared with cell salvage alone or control	Length of hospital stay (median [IQR]), days	170 (147.1 to 221.6)	Cell salvage: 160.7 (145.5 to 198.8) Control: 168.9 (140.3 to 219.3)	Kruskal-Wallis P-value=0.724	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	ANH and intraoperative cell salvage[1]	Length of hospital stay (median [IQR]), days	10 (8 to 13)	9 (7 to 12)	P=0.17	

Abbreviations: ANH, acute normovolemic haemodilution; IQR, interquartile range.

[1] Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.

Key question(s): In patients undergoing surgery, what is the effect of perioperative ANH and intraoperative cell salvage on ICU length of stay?		Evidence table ref*: POQ3.I3.S6
1. Evidence base		
Two level II studies: McGill 2002 (fair quality; N=254); Wong 2002 (fair quality; N=145)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Both studies are consistent in finding no significant difference between treatment arms.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
McGill 2002 (median [IQR]) Length of ICU stay (ANH + cell salvage vs. control): 23.3 (22.5 to 25.0) vs. 22.9 (21.8 to 24.5); P=NR Length of ICU stay (ANH + cell salvage vs. cell salvage alone): 23.3 (22.5 to 25.0) vs. 22.7 (22.0 to 24.6); P=NR Kruskal-Wallis P-value=0.249 Wong (2002) (median [IQR], ANH +cell salvage vs. control) Length of ICU stay: 1 (0 to 25) vs. 1 (0 to 25); P=0.89	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
McGill 2002 was conducted in patients undergoing cardiac surgery and Wong 2002 was conducted in patients undergoing aortic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Both studies were conducted in a UK hospital setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two fair quality level II studies, with a moderate risk of bias.
2. Consistency	A	Both studies consistent.
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied. One study was in cardiac study and the other in aortic surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. Both studies were conducted in the UK.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on ICU length of stay is uncertain.

Abbreviations: ANH, acute normovolemic haemodilution; ICU, intensive care unit; IQR, interquartile range.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I3.S6 Characteristics and results of studies examining the effect of perioperative ANH and intraoperative cell salvage on length of ICU stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
McGill (2002)	Level II *Fair*	N=254	Adults undergoing cardiac surgery	UK hospital	ANH and intraoperative cell salvage compared with cell salvage alone or control	Length of ICU stay (median [IQR]), days	23.3 (22.5 to 25.0)	Cell salvage: 22.7 (22.0 to 24.6) Control: 22.9 (21.8 to 24.5)	Kruskal-Wallis P-value=0.249	
Wong (2002)	Level II *Fair*	N=145	Adults undergoing aortic surgery	UK hospital	ANH and intraoperative cell salvage[1]	Length of ICU stay (median [IQR]), days	1 (0 to 25)	1 (0 to 25)	P=0.89	

Abbreviations: ANH, acute normovolemic haemodilution; ICU, intensive care unit; IQR, interquartile range.

[1] Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. Blood lost during the procedure was salvaged. All autologous blood (ANH and salvaged) was reinfused within 6 hours of withdrawal.

Recommendation(s) for acute normovolemic haemodilution combined with intraoperative cell salvage

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
No recommendation made for this combined intervention. See individual recommendations for intervention 1 (acute normovolemic haemodilution) and intervention 2 (intraoperative cell salvage).		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?	YES	NO

Intervention 4 – Postoperative cell salvage

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on transfusion incidence?		Evidence table ref*: POQ3.I4.P1
1. Evidence base		
1 level I study: Carless 2006: good quality; includes 18 RCTs[1] (N=1462): 10 cardiac and 8 orthopaedic (all fair quality) 3 level II studies published after the Carless 2006 search date: Amin 2008 (orthopaedic surgery; fair quality; N=178); Cheng 2005 (orthopaedic surgery; fair quality; N=60); Zacharopoulos 2007 (orthopaedic surgery; poor quality; N=60)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
There is a significant degree of heterogeneity within the trials in Carless 2006 (Phet<0.00001). The impact of postoperative cell salvage is significant for all of the subgroups analysed in Carless 2006 except studies without a transfusion protocol. In all three of the RCTs uncovered in the SR conducted herein, cell salvage had no impact on transfusion incidence.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained (orthopaedic)
	C	Some inconsistency, reflecting genuine uncertainty around question (cardiac)
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
A meta-analysis was conducted using the data from Carless 2006 and the three RCTs uncovered in the systematic review conducted herein. All surgery types – RR 0.60 (0.47, 0.77); 21 trials (N=1760) Cardiac surgery – RR 0.86 (0.74, 1.00); 10 trials (N=743) Orthopaedic surgery – RR 0.37 (0.24, 0.55); 11 trials (N=1017) Studies with a transfusion protocol – RR 0.66 (0.52, 0.85); 17 trials (N=1375) Studies without a transfusion protocol – RR 0.21 (0.03, 1.70); 4 trials (N=385)	A	Very large (orthopaedic)
	B	Substantial
	C	Moderate
	D	Slight/Restricted (cardiac)
4. Generalisability		
All the studies were conducted in patients undergoing cardiac surgery or orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Most of the studies were conducted in developed countries. Zacharopoulos 2007 was conducted in a small town in Greece with approximately 8000 inhabitants. Exclusion of this study from the meta-analysis does not impact the results.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Carless 2006 included several older studies. The CRG noted that cell salvage technology has changed over time. The transfusion triggers within these studies have also changed over this time.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Cardiac	TKA	Description
1. Evidence base	C	C	One good quality level I study of fair quality level II studies and three subsequently published fair-to-poor quality level II studies.
2. Consistency	C	B	In cardiac evidence there is some inconsistency reflecting genuine uncertainty. In TKA most studies consistent and inconsistency can be explained
3. Clinical impact	D	A	Slight impact in cardiac surgery and a very large impact in TKA.
4. Generalisability	B	B	Evidence directly generalisable to target population (with some caveats for cardiac).
5. Applicability	B	B	Evidence applicable to Australian healthcare context with few caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing total knee arthroplasty, postoperative cell salvage reduces the incidence of allogeneic blood transfusion.

In adult patients undergoing cardiac surgery, postoperative cell salvage may reduce the incidence of allogeneic blood transfusion.

Abbreviations: RCT, randomised controlled trial; RR, relative risk; SR, systematic review; TKA, total knee arthroplasty.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I4.P1 Characteristics and results of studies examining the effect of postoperative cell salvage on transfusion incidence.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I Good	18 trials (fair quality) N=1462	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Patients transfused with allogeneic blood	287/738 (39%)	473/724 (65%)	P=0.0002	Phet<0.00001
Amin (2008)	Level II Fair	N=178	Adults undergoing unilateral TKA	Hospital in UK	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Patients transfused with allogeneic blood	12/92 (13%)	13/86 (15%)	P=0.69	
Cheng (2005)	Level II Fair	N=60	Adults undergoing TKA	Hospital in Hong Kong	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Patients transfused with allogeneic blood	4/26 (15%)	13/34 (38%)	P=0.07	
Zacharopoulos (2007)	Level II Poor	N=60	Adults undergoing TKA	The study was conducted in a small town of ~8000 inhabitants in Greece	Postoperative cell salvage and reinfusion of washed blood within 6 hours of operation.	Patients transfused with allogeneic blood	5/30 (17%)	10/30 (33%)	P=0.15	
Cardiac surgery										
Carless (2006)	Level I *Good*	10 trials (fair quality) N=743	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Patients transfused with allogeneic blood	232/375 (62%)	275/368 (75%)	P=0.05	Phet=0.0001
Orthopaedic surgery										
Carless (2006)	Level I *Good*	8 trials (fair quality) N=719	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Patients transfused with allogeneic blood	55/363 (15%)	198/356 (56%)	P<0.00001	Phet=0.002
Studies with a transfusion protocol										
Carless (2006)	Level I *Good*	15 trials (fair quality) N=1137	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Patients transfused with allogeneic blood	233/576 (40%)	348/561 (62%)	P=0.002	Phet<0.00001

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Studies without a transfusion protocol										
Carless (2006)	Level I *Good*	3 trials (fair quality) N=179	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Patients transfused with allogeneic blood	54/162 (33%)	125/163 (77%)	P=0.27	Phet<0.00001

Abbreviations: TKA, total knee arthroplasty

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on transfusion volume?		Evidence table ref*: POQ3.I4.P2
1. Evidence base		
1 level I study: Carless 2006: good quality; includes 9 RCTs[1] (N=689): 7 cardiac and 2 orthopaedic (all fair quality) 3 level II studies published after the Carless 2006 search date: Amin 2008 (orthopaedic; fair quality; N=178); Cheng 2005 (orthopaedic; fair quality; N=60); Zacharopoulos 2007 (orthopaedic; poor quality; N=60). NB: none of the three RCTs above provided enough information to conduct a meta-analysis. Similarly none of the studies provided enough detail to determine whether the differences in the point estimates between the treatment arms is statistically significant.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
There is a significant degree of heterogeneity between the studies (Phet=0.03). When the studies are limited to those using a transfusion protocol the heterogeneity is no longer significant (Phet=0.09). The impact of postoperative cell salvage is significant for all of the subgroups analysed in Carless 2006. The results of the RCTs published after Carless 2006 are consistent in direction.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless 2006 All surgery types – mean difference -0.82 units (-1.12, -0.51); 9 trials (N=689) Cardiac surgery – mean difference -0.83 units (-1.25, -0.40); 7 trials (N=580) Orthopaedic surgery – mean difference -0.80 units (-1.17, -0.43); 2 trials (N=109)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The studies were conducted in patients undergoing cardiac and orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One good quality level I study (included studies were of fair quality)
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	Moderate impact in cardiac and orthopaedic surgery
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery or total knee arthroplasty, postoperative cell salvage reduces the volume of allogeneic blood transfusion.

Abbreviations: RCT, randomised controlled trial.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] All the studies were fair quality.

POQ3.I4.P2 Characteristics and results of studies examining the effect of postoperative cell salvage on transfusion volume.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I Good	9 trials (fair quality) N=689	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), units	-0.82 (-1.12, -0.51)		P<0.00001	Phet=0.03
Amin (2008)	Level II Fair	N=178	Adults undergoing unilateral TKA	Hospital in UK	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Total units of allogeneic blood transfused	22	26	NR	
Cheng (2005)	Level II Fair	N=60	Adults undergoing TKA	Hospital in Hong Kong	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Mean (SD) units of allogeneic blood transfused	0.15 (0 to 1)	0.46 (0 to 4)	P=0.033	
Zacharopoulos (2007)	Level II Poor	N=60	Adults undergoing TKA	The study was conducted in a small town of ~8000 inhabitants in Greece	Postoperative cell salvage and reinfusion of washed blood within 6 hours of operation.	Median (IQR) units of allogeneic blood transfused	0.3 (NR)	1.5 (NR)	NR	
Cardiac surgery										
Carless (2006)	Level I *Good*	7 trials (fair quality) N=580	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), units	-0.83 (-1.25, -0.40)		P=0.0001	Phet=0.01
Orthopaedic surgery										
Carless (2006)	Level I *Good*	2 trials (fair quality) N=109	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), units	-0.80 (-1.17, -0.43)		P<0.0001	Phet=1.00
Studies with a transfusion protocol										
Carless (2006)	Level I *Good*	6 trials (fair quality) N=398	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), units	-0.75 (-1.02, -0.47)		P<0.00001	Phet=0.09
Studies without a transfusion protocol										
Carless (2006)	Level I *Good*	3 trials (fair quality) N=291	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), units	-1.64 (-2.96, -0.33)		P=0.01	Phet=0.05

Abbreviations: CI, confidence interval; IQR, interquartile range; NR, not reported; SD, standard deviation; TKA, total knee arthroplasty.

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on blood loss?		Evidence table ref*: POQ3.I4.P3
1. Evidence base		
1 level I study: Carless 2006 (good quality; includes 8 RCTs[1]; N=555) 1 level II studies published after the Carless 2006 search date: Cheng 2005 (fair quality; N=60; patients undergoing TKA)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The degree of heterogeneity within the trials in Carless 2006 is not significant (Phet=0.12). The lack of impact of postoperative cell salvage on blood loss is consistent across cardiac and orthopaedic surgery. Carless 2006 reported total blood loss whilst Cheng 2005 reported operative blood loss.	A	All studies consistent in finding no difference
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless 2006 All surgery types – mean difference -56.97 mL (-152.05, 38.12); 8 trials (N=555) Cardiac surgery – mean difference -85.04 mL (-212.50, 42.41); 5 trials (N=366) Orthopaedic surgery – mean difference -21.74 mL (-164.51, 121.04); 2 trials (N=189) Cheng 2005 Median (IQR), cell salvage vs. control: 273 (100 to 600) vs. 280 (100 to 800); P=0.84	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
All the studies were conducted in patients undergoing cardiac surgery or orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One good quality level I study (included studies were of fair quality) and one subsequently published fair quality level II study.
2. Consistency	A	All studies consistent in finding no difference.
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	B	Evidence directly generalisable to target population with some caveats.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery or total knee arthroplasty, postoperative cell salvage does not appear to have an effect on total blood loss.

Abbreviations: RCT, randomised controlled trial; TKA, Total knee arthroplasty.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] All the studies were fair quality.

POQ3.I4.P1 Characteristics and results of studies examining the effect of postoperative cell salvage on blood loss.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I Good	8 trials (fair quality) N=555	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Total blood loss, mL Mean difference (95% CI)	-56.97 (-152.05, 38.12)		P=0.24	Phet=0.12
Cheng (2005)	Level II Fair	N=60	Adults undergoing TKA	Hospital in Hong Kong	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Operative blood loss, mL Median (IQR)	273 (100 to 600)	280 (100 to 800)	P=0.84	
Cardiac surgery										
Carless (2006)	Level I *Good*	5 trials (fair quality) N=366	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Total blood loss, mL Mean difference (95% CI)	-85.04 (-212.50, 42.41)		P=0.19	Phet=0.03
Orthopaedic surgery										
Carless (2006)	Level I *Good*	3 trials (fair quality) N=189	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Total blood loss, mL Mean difference (95% CI)	-21.74 (-164.51, 121.04)		P=0.77	Phet=0.81

Abbreviations: CI, confidence interval; IQR, interquartile range; TKA, total knee arthroplasty.

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on mortality?		Evidence table ref*: POQ3.I4.P4
1. Evidence base		
1 level I study: Carless 2006 (good quality; includes 5 RCTs all of fair quality; N=471). All the studies were in patients undergoing cardiac surgery.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
There is no significant heterogeneity between the studies (Phet=0.92). All of the studies are consistent in finding that cell salvage had no significant impact.	A	All studies consistent in finding no difference
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
RR 1.64 (0.52, 5.17)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
All of the five studies that reported mortality as an outcome were conducted in patients undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All of the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Included studies were underpowered to detect a mortality difference. Transfusion is a confounder for this outcome.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One good quality level I study (included studies were of fair quality).
2. Consistency	A	All studies consistent in finding no difference.
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	B	Evidence not directly generalisable to the target population but could be sensibly applied. Only includes patients undergoing cardiac surgery.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of postoperative cell salvage on mortality is uncertain.

Abbreviations: RCT, randomised controlled trial; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I4.P4 Characteristics and results of studies examining the effect of postoperative cell salvage on mortality.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I Good	5 trials N=471	Adults undergoing any elective surgery. All of the 5 studies that reported mortality as an outcome were conducted in patients undergoing cardiac surgery.	All studies conducted in developed countries	Postoperative cell salvage	Mortality	8/246 (3%)	4/225 (2%)	P=0.40	Phet=0.92

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on morbidity?		Evidence table ref*: POQ3.I4.P5
1. Evidence base		
1 level I study: Carless (good quality) – infection (5 RCTs; 3 cardiac and 2 orthopaedic; N=429); wound complication (6 RCTs; 4 cardiac and 2 orthopaedic; N=404); any thrombosis (4 RCTs; all orthopaedic; N=240); stroke (1 RCT; cardiac; N=30); non-fatal MI (2 RCTs; both cardiac; N=144); DVT (3 RCTs; all orthopaedic; N=210). All the RCTs were fair quality 2 level II studies published after the Carless 2006 search date: Amin 2008 (orthopaedic; fair quality; N=178) – wound infection; infections other than wound infection; DVT; persistent wound drainage (no infection) Cheng 2005 (orthopaedic; fair quality; N=60) – febrile complications	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The heterogeneity within trials in Carless 2006 is not significant. The lack of impact of postoperative cell salvage is consistent across patients undergoing cardiac surgery and orthopaedic surgery.	A	All studies consistent in finding no difference.
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless 2006 Infection: RR 0.60 (0.17, 2.15); wound complication: RR 0.84 (0.37, 1.92); any thrombosis: RR 1.41 (0.43, 4.57); stroke: RR 3.00 (0.13, 68.26); non-fatal MI: RR 0.85 (0.25, 2.93); DVT: RR 0.64 (0.15, 2.66) Amin 2008 Wound infection: RR 1.40 (0.24, 8.19); infections other than wound infection: RR 0.93 (0.13, 6.49); DVT: RR 0.47 (0.04, 5.06); persistent wound drainage (no infection): RR 1.87 (0.17, 20.25) Cheng 2005 Febrile complications: RR 2.62 (0.25, 27.30)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
All the studies were conducted in patients undergoing cardiac surgery or orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All of the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

CRG considered washed vs. unwashed to be important for this outcome. Carless 2006 did not report washed vs. unwashed for morbidity.

Carless 2006 included several older studies. The CRG noted that cell salvage technology has changed over time.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One good quality level I study (included studies were of fair quality) and two subsequently published fair quality level II studies.
2. Consistency	A	All studies consistent in finding no difference
3. Clinical impact	D	No difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery or total knee arthroplasty, postoperative cell salvage does not appear to have an effect on morbidity, including infection.

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; RCT, randomised controlled trial; RR, relative risk.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I4.P5 Characteristics and results of studies examining the effect of postoperative cell salvage on morbidity.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I Good	5 trials (fair quality) N=429	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Infection	7/210 (3%)	17/219 (8%)	P=0.43	Phet=0.26
		6 trials (fair quality) N=404	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Wound complication	11/213 (5%)	11/191 (6%)	P=0.69	Phet=0.63
		4 trials (fair quality) N=240	Adults undergoing any elective surgery.	All studies conducted in developed countries	Postoperative cell salvage	Any thrombosis	6/120 (5%)	4/120 (3%)	P=0.57	Phet=0.83
		1 trial (fair quality) N=30	Adults undergoing any elective surgery.	All studies conducted in developed countries	Postoperative cell salvage	Stroke	1/15 (7%)	0/15 (0%)	P=0.49	Phet=NA
		2 trials (fair quality) N=144	Adults undergoing any elective surgery.	All studies conducted in developed countries	Postoperative cell salvage	Non-fatal MI	5/71 (7%)	6/73 (8%)	P=0.80	Phet=0.94
		3 trials (fair quality) N=210	Adults undergoing any elective surgery.	All studies conducted in developed countries	Postoperative cell salvage	DVT	3/105 (3%)	5/105 (5%)	P=0.54	Phet=0.46
Amin (2008)	Level II Fair	N=178	Adults undergoing unilateral TKA	Hospital in UK	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Wound infection	3/92 (3%)	2/86 (2%)	P=0.71	
						Infections other than wound infection	2/92 (2%)	2/86 (2%)	P=0.95	
						DVT	1/92 (1%)	2/86 (2%)	P=0.53	
						Persistent wound drainage (no infection)	2/92 (2%)	1/86 (1%)	P=0.61	
Cheng (2005)	Level II Fair	N=60	Adults undergoing TKA	Hospital in Hong Kong	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Febrile complications	2/26 (8%)	1/34 (3%)	P=0.403	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Cardiac surgery										
Carless (2006)	Level I *Good*	3 trials (fair quality) N=259	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Infection	4/125 (3%)	13/134 (10%)	P=0.53	Phet=0.14
		4 trials (fair quality) N=264	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Wound complication	6/143 (4%)	5/121 (4%)	P=0.88	Phet=0.33
		1 trial (fair quality) N=30	Adults undergoing any elective surgery. The only trial that reported incidence of stroke as an outcome was in patients undergoing cardiac surgery.	All studies conducted in developed countries	Postoperative cell salvage	Stroke	1/15 (7%)	0/15 (0%)	P=0.49	Phet=NA
		2 trials (fair quality) N=144	Adults undergoing any elective surgery. All of the trials that reported incidence of non-fatal MI as an outcome were in patients undergoing cardiac surgery.	All studies conducted in developed countries	Postoperative cell salvage	Non-fatal MI	5/71 (7%)	6/73 (8%)	P=0.80	Phet=0.94
Orthopaedic surgery										
Carless (2006)	Level I *Good*	2 trials (fair quality) N=170	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Infection	3/85 (4%)	4/85 (5%)	P=0.78	Phet=0.28
		2 trials (fair quality) N=140	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Wound complication	5/70 (7%)	6/70 (9%)	P=0.73	Phet=0.88
		4 trials (fair quality) N=240	Adults undergoing any elective surgery. All of the trials that reported incidence of thrombosis as an outcome were in patients undergoing orthopaedic surgery.	All studies conducted in developed countries	Postoperative cell salvage	Any thrombosis	6/120 (5%)	4/120 (3%)	P=0.57	Phet=0.83
		3 trials (fair quality) N=210	Adults undergoing any elective surgery. All of the trials that reported incidence of DVT as an outcome were in patients undergoing orthopaedic surgery.	All studies conducted in developed countries	Postoperative cell salvage	DVT	3/105 (3%)	5/105 (5%)	P=0.54	Phet=0.46

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; NA, not applicable; TKA, total knee arthroplasty.

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on quality of life?		Evidence table ref*: POQ3.I4.P5
1. Evidence base		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of postoperative cell salvage on quality of life is unknown.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on change in haemoglobin concentration?		Evidence table ref*: POQ3.I4.S1
1. Evidence base		
3 level II studies: Amin 2008 (orthopaedic; fair quality; N=178); Cheng 2005 (orthopaedic; fair quality; N=60); Zacharopoulos 2007 (orthopaedic; poor quality; N=60)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All three RCTs are consistent in finding that postoperative cell salvage had no significant impact on change in Hb concentration.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Amin 2008 – mean (SD), treatment vs. control: 2.2 (0.7) vs. 2.6 (0.8); P=0.354 Cheng 2005 – Median (IQR): 101 (84 to 128) vs. 104 (87 vs. 137); P=0.332 Zacharopoulos 2007 – No significant difference (no more detail provided)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
All three studies were conducted in patients undergoing TKA.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Amin 2008 was conducted in the UK, Cheng 2005 was conducted in Hong Kong, and Zacharopoulos 2007 was conducted in a small town in Greece with approximately 8000 inhabitants. The exclusion of Zacharopoulos 2007 does not influence the outcome.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Three fair-to-poor quality level II studies.
2. Consistency	A	All studies consistent.
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing total knee arthroplasty, the effect of postoperative cell salvage on haemoglobin concentration is uncertain.

Abbreviations: Hb, haemoglobin; IQR, interquartile range; RCT, randomised controlled trial; SD, standard deviation; TKA, total knee arthroplasty.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I4.S1 Characteristics and results of studies examining the effect of postoperative cell salvage on change in haemoglobin.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Amin (2008)	Level II Fair	N=178	Adults undergoing unilateral TKA	Hospital in UK	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Mean (SD) change in Hb concentration (pre- vs. postoperative 24, 48, 72 hr), g/dL	2.2 (0.7)	2.6 (0.8)	P=0.354	
Cheng (2005)	Level II Fair	N=60	Adults undergoing TKA	Hospital in Hong Kong	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Mean (range) haemoglobin level immediately postoperative, g/dL	101 (84 to 128)	104 (87 to 137)	P=0.332	
						Mean (range) haemoglobin level 3 days postoperative, g/dL	98 (77 to 130)	101 (77 to 130)	P=0.401	
Zacharopoulos (2007)	Level II Poor	N=60	Adults undergoing TKA	The study was conducted in a small town of ~8000 inhabitants in Greece	Postoperative cell salvage and reinfusion of washed blood within 6 hours of operation.	Mean (SD) change in Hb concentration (pre- vs. postoperative Day 1, 5, 15)	NR	NR	NS	

Abbreviations: Hb, haemoglobin concentration; NR, not reported; NS, not significant; SD, standard deviation; TKA, total knee arthroplasty.

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on reoperation for bleeding?		Evidence table ref*: POQ3.I4.S2
1. Evidence base		
1 level I study: Carless 2006 (good quality; includes 6 RCTs- all fair quality, all cardiac surgery; N=374) No Level II evidence published after Carless 2006.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The degree of heterogeneity within the trials in Carless 2006 is not significant (Phet=0.54).	A	All studies consistent in finding no difference
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless 2006 – RR 1.41 (0.53, 3.78)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability		
All the trials in Carless 2006 were in patients undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All of the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One good quality level I study (included studies were of fair quality) and one subsequently published fair quality level II study.
2. Consistency	A	All studies consistent in finding no difference
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	B	Evidence directly generalisable to target population with some caveats.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of postoperative cell salvage on risk of reoperation for bleeding is uncertain.

Abbreviations: RCT, randomised controlled trial; RR, relative risk; TKA, total knee arthroplasty.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[1] All the studies were fair quality.

POQ3.I4.S2 Characteristics and results of studies examining the effect of postoperative cell salvage on reoperation for bleeding.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I Good	6 trials (fair quality) N=374	Adults undergoing any elective surgery. All of the trials that reported reoperation for bleeding as an outcome were conducted in patients undergoing cardiac surgery.	All studies conducted in developed countries	Postoperative cell salvage	Patients who underwent reoperation for bleeding	11/193 (6%)	6/181 (3%)	P=0.50	Phet=0.54

Abbreviations: TKA, total knee arthroplasty.

Key question(s): In patients undergoing surgery, what is the effect of postoperative cell salvage on length of hospital stay?		Evidence table ref*: POQ3.I4.S5
1. Evidence base		
1 level I study: Carless 2006 (good quality; includes 4 RCTs; 3 cardiac and 1 orthopaedic (all fair quality); N=297 Level II study published after the Carless 2006 search date: Amin 2008 (fair quality; N=178)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The degree of heterogeneity within the trials in Carless 2006 is not significant (Phet=0.11). The results in Carless 2006 are consistent across both cardiac and orthopaedic surgery. The results from Amin 2008 are not consistent with the results from Carless 2006.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Carless 2006 mean difference -1.72 days (-2.82, -0.62) Amin 2008 Median (IQR), cell salvage: 6.6 days (3 to 14) vs. 7.0 days (3 to 16); P=0.54	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
The trials in Carless 2006 were conducted in patients undergoing cardiac and patients undergoing orthopaedic surgery. Amin 2008 was conducted in patients undergoing TKA.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies were conducted in developed countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Applicability depends on regional practice (rehabilitation varies between institutions).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Three level II studies with a moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	C	Moderate clinical impact
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery and total knee arthroplasty, postoperative cell salvage may reduce length of hospital stay.

Abbreviations: IQR, interquartile range; RCT, randomised controlled trial; TKA, total knee arthroplasty.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I4.S5 Characteristics and results of studies examining the effect of postoperative cell salvage on length of hospital stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Carless (2006)	Level I Good	4 trials (fair quality) N=297	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), days	-1.72 (-2.82, -0.62)		P=0.002	Phet=0.11
Amin (2008)	Level II Fair	N=178	Adults undergoing unilateral TKA	Hospital in UK	Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery.	Median (IQR) difference, days	6.6 (3 to 14)		7.0 (3 to 16)	P=0.54
Cardiac surgery										
Carless (2006)	Level I *Good*	3 trials (fair quality) N=227	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), days	-1.41 (-2.69, -0.13)		P=0.03	Phet=0.08
Orthopaedic surgery										
Carless (2006)	Level I *Good*	1 trial (fair quality) N=70	Adults undergoing any elective surgery	All studies conducted in developed countries	Postoperative cell salvage	Mean difference (95% CI), days	-2.60 (-4.76, -0.44)		P=0.02	Phet=NA

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable; TKA, total knee arthroplasty.

Recommendation(s) for postoperative cell salvage

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In adult patients undergoing cardiac surgery or total knee arthroplasty, in whom significant postoperative blood loss is anticipated, postoperative cell salvage should be considered.	C	PO3.I4.P1, PO3.I4.P2, PO3.I4.P5, PO3.I4.S5

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Postoperative cell salvage use will increase (not widely used at present).		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Training and equipment costs.		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Changes in organisation of postoperative care which will have nursing resource implications in postoperative wards.		
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Initial capital investment; recurrent expenditure (but preservation of blood supply at ARCBS level, which results in cost-shifting from Commonwealth to State); only applicable when postoperative drainage utilised; may not be widely supported by orthopaedic surgeons.		
What could help to facilitate implementation of the recommendation?	YES	NO
Development of local policies for postoperative cell salvage; lobbying for funding of cell salvage device.		

Intervention 5 – Deliberate induced hypotension

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on transfusion incidence?		Evidence table ref*: POQ3.I5.P1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Five level II studies: 3 good quality RCTs, 2 fair quality RCTs.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
4 RCTs examined prostatectomy patients and reported a significant effect. Important to note that 3 of the RCTs were conducted at the same institution, not possible to ascertain if there was an overlap in study population. 1 RCT examined lienorenal shunt surgery and did not observe a significant effect, however the sample size was small (N=18). Test of heterogeneity across the 5 RCTs was not significant (P=0.14).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Meta-analysis of 5 RCTs revealed a risk ratio of 0.38 (95%CI 0.19, 0.75), P=0.005. This shows that the incidence of blood transfusion was 62% lower in patients with induced hypotension.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
As 4 of the 5 studies examined patients undergoing prostatectomy. Consequently, the evidence is likely generalisable to patients undergoing this surgical procedure.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The 4 RCTs examining prostatectomy were conducted in Germany and Canada, these findings are likely applicable to Australia. The RCT examining Lienorenal shunt surgery was conducted in India, which limits its applicability in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Three publications (Boldt et al., Piper et al. and Suttner et al.) were conducted at the same institution. However, based on information in the publications, it is not possible to determine if there was an overlap in the study populations. Consequently, lack of independence should be considered during the interpretation of the results from these three studies.
Given the concerns regarding generalisability and applicability, the recommendation was graded 'C'.
The Clinical/Consumer Reference Group (CRG) noted the study by Sood et al. had a small sample size, was conducted in India, and examined lienorenal shunt surgery. Consequently, the findings from this study were not considered by the CRG in assessing the effect of induced hypotension on transfusion incidence.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	Three RCTs of good quality and two of fair quality.
2. Consistency	B	Test of heterogeneity across the five RCTs was not significant.
3. Clinical impact	A	Meta-analysis of the five RCTs revealed a risk ratio of 0.38 (95%CI 0.19, 0.75), P=0.005.
4. Generalisability	C	The evidence is likely generalisable to patients undergoing prostatectomy.
5. Applicability	C	The four studies that examined prostatectomy patients were conducted in Germany and Canada, as such the findings are likely applicable in the Australian context. The study that examined lienorenal shunt surgery was conducted in India, which limits the applicability of the evidence in Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing radical prostatectomy, deliberate induced hypotension (mean arterial pressure 50–60 mmHg) reduces the incidence of allogeneic RBC transfusion.

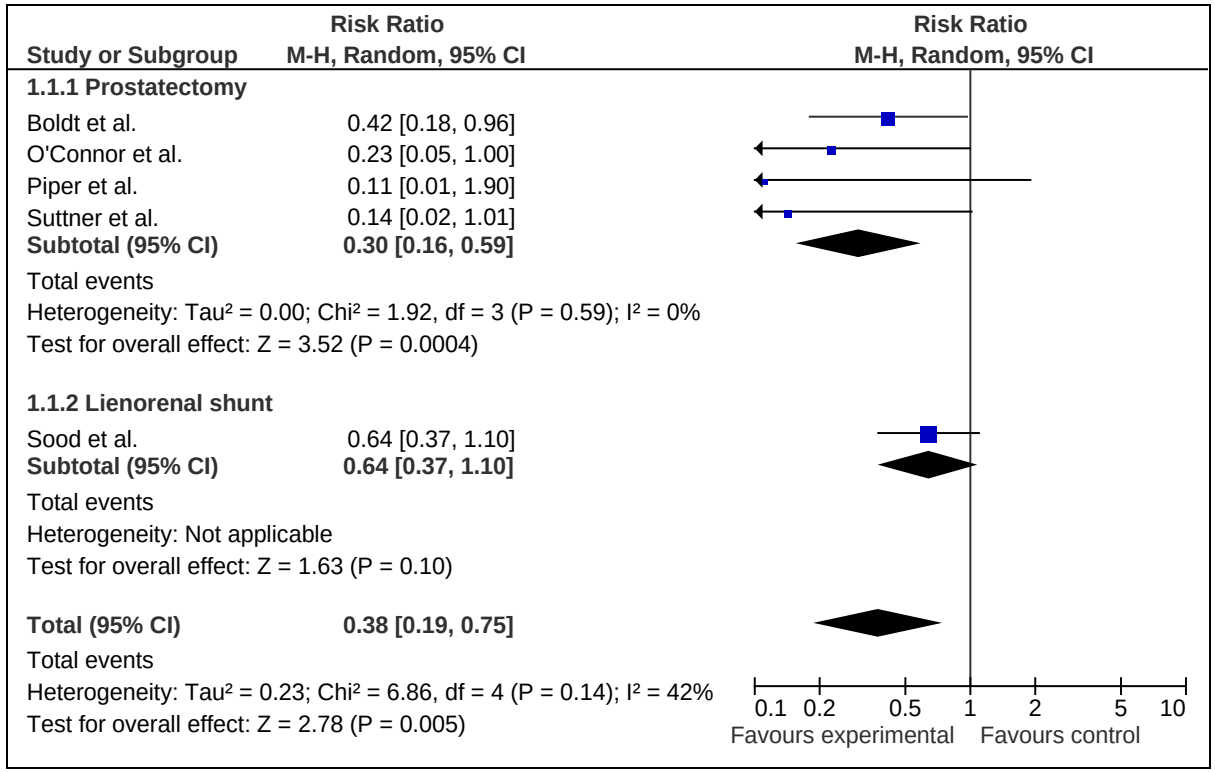
POQ3.I5.P1 Characteristics and results of studies examining the effect of deliberate induced hypotension on transfusion incidence

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Prostatectomy										
O'Connor et al. (2006)	Level II *Good*	N=99	Patients with adenocarcinoma of the prostate to undergo radical retropubic prostatectomy.	Medical Institution in Canada.	Hypotension induced using epidural and ropivacaine (MAP 55-60mmHg)	Incidence of blood transfusion n/N (%)	2/49 (4%)	9/50 (18%)	0.028	See meta-analysis of effect
Piper et al. (2002)	Level II *Fair*	N=30	Patients undergoing elective radical prostatectomy (ASA class II and III only).	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Incidence of blood transfusion n/N (%)	0/15 (0%)	4/15 (27%)	<0.05	
Suttner et al. (2001)	Level II *Good*	N=28	Patients undergoing elective radical prostatectomy.	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Incidence of blood transfusion n/N (%)	1/14 (7%)	7/14 (50%)	<0.05	
Boldt et al. (1999)	Level II *Good*	N=40	Patients under the age of 75 years undergoing retropubic radical prostatectomy with bilateral pelvic lymphadenectomy.	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Incidence of blood transfusion n/N (%)	5/20 (25%)	12/20 (60%)	<0.05	
Lienorenal shunt surgery										
Sood et al. (1987)	Level II *Fair*	N=18	Patients undergoing elective, proximal, lienorenal shunts for portal hypertension.	Hospital in India.	Controlled hypotension (Systolic BP 90-95mmHg) using sodium nitroprusside	Incidence of blood transfusion n/N (%)	5/8 (63%)	10/10 (100%)	NR	

Abbreviations: ASA, American Society of Anaesthesiologists; BP, blood pressure; MAP, mean arterial pressure; NR, not reported.

[a] Three publications (Boldt et al., Piper et al. and Suttner et al.) were conducted at the same institution. However, based on information in the publications, it is not possible to determine if there was an overlap in the study populations. Consequently, lack of independence should be considered during the interpretation of the results from these three studies.

Meta-analysis of the effect of induced hypotension on the incidence of blood transfusion.



Meta-analysis shows that the incidence of blood transfusion was 62% lower in patients with induced hypotension, compared to patients with normotension.

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on transfusion volume?		Evidence table ref*: POQ3.I5.P2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study: systematic review with good quality rating, low risk of bias. 7 level II studies: 3 good quality RCTs, 4 fair quality RCTs.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Systematic review conducted a meta-analysis and found a significant reduction in transfusion volume in patients with induced hypotension. Test of heterogeneity was significant (P<0.05). 4 RCTs examined prostatectomy patients and reported a significant reduction in transfusion volume. Important to note that 3 of the RCTs were conducted at the same institution (see other factors). 2 RCTs examined patients undergoing hip arthroplasty, one observed a significant reduction. 1 RCT examined patients undergoing lienorenal shunt surgery and observe a significant reduction.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Meta-analysis: Systematic review estimated that in orthopaedic surgical patients, blood transfusion was 667mL (95%CI 370, 963) lower in patients with induced hypotension. Use of different units and measurements made it difficult to synthesize a single effect estimate across the RCTs identified.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to patients undergoing major joint replacement surgery and prostatectomy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Most of the studies included in the systematic review were conducted in Europe, US and Canada. The 2 RCTs examining hip arthroplasty were conducted in Turkey and Sweden, while the 4 RCTs examining prostatectomy were conducted in Germany and Canada. As such it is likely that these findings are applicable in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Three publications (Boldt et al., Piper et al. and Suttner et al.) were conducted at the same institution. However, based on information in the publications, it is not possible to determine if there was an overlap in the study populations. Consequently, lack of independence should be considered during the interpretation of the results from these three studies.
The Clinical/Consumer Reference Group (CRG) noted the study by Sood et al. had a small sample size, was conducted in India, and examined lienorenal shunt surgery. Consequently, the CRG did not consider the findings from this study in assessing the effect of induced hypotension on transfusion incidence.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	One systematic review of good quality. Three RCTs of good quality and four RCTs of fair quality.
2. Consistency	A	Induced hypotension was found to significantly reduce transfusion volume in all studies except for one RCT, conducted in Turkey with a small sample size (N=20).
3. Clinical impact	B	Meta-analysis estimated that in major joint surgery, blood transfusion was 667mL lower in patients with induced hypotension.
4. Generalisability	B	The evidence is likely generalisable to patients undergoing major joint replacement surgery and prostatectomy.
5. Applicability	B	The studies identified were mostly conducted in developed western countries, similarly developed to Australia. As such, the findings are likely applicable in the Australian context.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing radical prostatectomy or major joint replacement, deliberate induced hypotension (MAP 50–60 mmHg) reduces the volume of allogeneic blood transfusion.

POQ3.I5.P2 Characteristics and results of studies examining the effect of deliberate induced hypotension on transfusion volume

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Orthopaedic surgery										
Paul et al. (2007)	Level I *Good*	6 (N=222)	Patients undergoing major joint replacement surgery	NR	Deliberate induced hypotension by any method	Blood transfused (mL) WMD (95%CI)	WMD: -667 mL (-963, -370)		NR	Search date: Up to Jan 2006
Karakaya et al. (1999)	Level II Fair	N=20	ASA class I and II patients undergoing primary total hip arthroplasty	Medical Institution in Turkey	Nitroglycerine induced hypotension (MAP 60-65mmhg)	Blood transfused per patient (Units) Mean (SD)	2.3 (0.8)	2.7 (1.1)	NS	Not included in Paul et al. as haemodilution was used concurrently
Fredin et al. (1984)	Level II Fair	N=57	Patients undergoing total hip arthroplasty.	Hospital in Sweden	Controlled hypotension (SBP 70-80mmHg) using sodium nitroprusside	Blood transfused per patient (mL) Mean (SD)	Intraop: 580 (380)	1210 (620)	<0.01	Not included in Paul et al. as all patients were also given blood thinners
							Total: 920 (580)	1540 (1050)	<0.01	
Prostatectomy										
O'Connor et al. (2006)	Level II *Good*	N=99	Patients with adenocarcinoma of the prostate to undergo radical retropubic prostatectomy.	Medical Institution in Canada.	Hypotension induced using epidural and ropivacaine (MAP 55-60mmHg)	Total volume of RBC transfused (Units)	3	24	NR	–
Piper et al. (2002)	Level II *Fair*	N=30	Patients undergoing elective radical prostatectomy (ASA class II and III only).	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Total volume of RBC transfused (Units)	0	10	P<0.05	–
Suttner et al. (2001)	Level II *Good*	N=28	Patients undergoing elective radical prostatectomy.	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Total volume of RBC transfused (Units)	3	17	P<0.05	–
Boldt et al. (1999)	Level II *Good*	N=40	Patients under the age of 75 years undergoing retropubic radical prostatectomy with bilateral pelvic lymphadenectomy.	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Total volume of RBC transfused (Units)	14	28	P<0.05	–

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Lienorenal shunt surgery										
Sood et al. (1987)	Level II *Fair*	N=18	Patients undergoing elective, proximal, lienorenal shunts for portal hypertension.	Hospital in India	Controlled hypotension (SBP 90-95mmHg) using sodium nitroprusside	Blood transfused per patient (Units) Mean (SD)	0.88 (0.9)	3.0 (1.2)	P<0.01	–

Abbreviations: ASA, American Society of Anaesthesiologists; BP, blood pressure; CI, confidence interval; MAP, mean arterial pressure; NR, not reported; NS, not statistically significant; RBC, red blood cells; SD, standard deviation; WMD, weighted mean difference.

[a] Three publications (Boldt et al., Piper et al. and Suttner et al.) were conducted at the same institution. However, based on information in the publications, it is not possible to determine if there was an overlap in the study populations. Consequently, lack of independence should be considered during the interpretation of the results from these three studies.

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on blood loss?		Evidence table ref*: POQ3.I5.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study: 1 systematic review with good quality rating. The systematic review reported non-significant bias (Egger's test P=0.955). Nine level II studies: 5 good quality RCTs, 4 fair quality RCTs.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The test of heterogeneity conducted by the systematic review was significant; this suggests that there may be differences between surgical methods and the methods of inducing hypotension. All RCTs, except 1 (Jacobi et al.), reported a significant reduction in blood loss among patients with induced hypotension. The study by Jacobi et al. examined patients undergoing endoscopic sinus surgery and had a small sample size (N=32), which may have contributed to the lack of a significant finding in the study.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Systematic review by Paul et al. estimated that in orthopaedic surgical patients, blood loss was lower by 286mL (95%CI 127, 447) in patients with induced hypotension. 8 RCTs provided sufficient data for meta-analysis, which showed that induced hypotension reduced blood loss by an average of 460mL (95%CI 210.9, 709.8), P=0.0003.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to patients undergoing orthopaedic surgery and prostatectomy. While the evidence is likely generalisable to all surgical procedures, the effect (reduction in blood loss) of the intervention would likely vary.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The systematic review included studies conducted mostly in Europe, US and Canada. The RCTs were conducted in Germany, Canada, Sweden, the Netherlands, Egypt and India. As such it is likely that these findings are applicable in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Three publications (Boldt et al., Piper et al. and Suttner et al.) were conducted at the same institution. However, based on information in the publications, it is not possible to determine if there was an overlap in the study populations. Consequently, lack of independence should be considered during the interpretation of the results from these three studies.

The Clinical/Consumer Reference Group noted the study by Sood et al. had a small sample size, was conducted in India and examined lienorenal shunt surgery. Consequently, the findings from this study were not considered in assessing the effect of induced hypotension on transfusion incidence.

The CRG also noted that the studies by Elsharnouby et al. and Jacobi et al. examined blood loss during endoscopic sinus surgery. In these studies, the importance of blood loss is related more to the obstruction of surgical field rather than to issues relating to blood transfusion requirements. Consequently, less emphasis has been placed on the findings from these studies.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	One good quality systematic review. Five RCTs of good quality and four RCTs of fair quality.
2. Consistency	A	All except one study showed that induced hypotension significantly reduced blood loss.
3. Clinical impact	B	The systematic review showed that induced hypotension reduces blood loss by 286mL (95%CI 127, 447) during orthopaedic surgery. Meta-analysis of the RCTs showed that induced hypotension reduced blood loss by 460mL (95%CI 210, 709).
4. Generalisability	B	The evidence is likely generalisable to patients undergoing major joint replacement surgery, breast reduction surgery and prostatectomy.
5. Applicability	B	The studies were mostly conducted in developed western countries, as such the evidence is likely applicable in the Australian context.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing radical prostatectomy, major joint replacement or breast reduction surgery, deliberate induced hypotension (MAP 50–60 mmHg) reduces the volume of blood loss.

POQ3.I5.P3 Characteristics and results of studies examining the effect of deliberate induced hypotension on blood loss

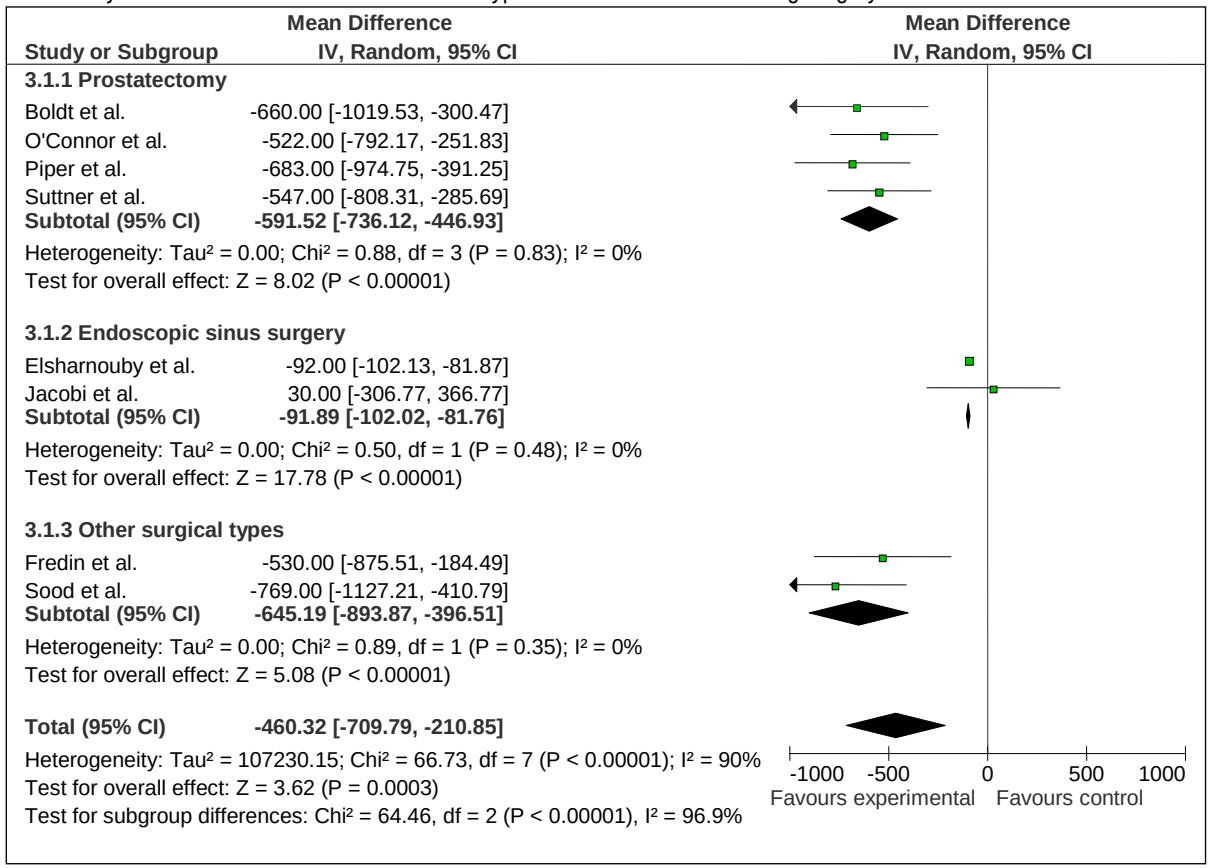
Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Orthopaedic surgery										
Paul et al. (2007)	Level I *Good*	17 (N=586)	Patients undergoing major joint replacement surgery.	NR	Deliberate induced hypotension by any method	Blood loss (mL) WMD (95%CI)	WMD: -286 (-447, -127)		NR	Search date: Up to Jan 2006
Fredin et al. (1984)	Level II *Fair*	N=57	Patients undergoing total hip arthroplasty.	Hospital in Sweden.	Controlled hypotension (SBP 70-80mmHg) using sodium nitroprusside	Blood loss (mL) Mean (SD)	Intraop: 620 (240)	1070 (630)	<0.001	Not included in Paul et al. as all patients were also given blood thinners
							Total: 1170 (395)	1700 (860)	<0.01	
Prostatectomy										
O'Connor et al. (2006)	Level II *Good*	N=99	Patients with adenocarcinoma of the prostate to undergo radical retropubic prostatectomy.	Medical Institution in Canada.	Hypotension induced using epidural and ropivacaine (MAP 55-60mmHg)	Blood loss (mL) Mean (SD)	955 (517)	1477 (823)	<0.001	See meta-analysis
Piper et al. (2002)	Level II *Fair*	N=30	Patients undergoing elective radical prostatectomy (ASA class II and III only).	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Blood loss (mL) Mean (SD)	843 (233)	1526 (409)	<0.05	
Suttner et al. (2001)	Level II *Good*	N=28	Patients undergoing elective radical prostatectomy.	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Blood loss (mL) Mean (SD)	788 (193)	1335 (460)	<0.05	
Boldt et al. (1999)	Level II *Good*	N=40	Patients under the age of 75 years undergoing retropubic radical prostatectomy with bilateral pelvic lymphadenectomy.	Hospital in Germany [a]	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Intraoperative and Total Blood loss (mL)	1260 (570)	1920 (590)	<0.05	

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Endoscopic sinus surgery										
Elsharnouby et al. (2006)	Level II *Good*	N=60	Patients undergoing functional endoscopic sinus surgery.	Hospital in Egypt.	Controlled hypotension (MAP 50-60mmHg) using magnesium sulphate	Blood loss (mL) Mean (SD)	165 (19)	257 (21)	<0.05	See meta-analysis
Jacobi et al. (2000)	Level II *Fair*	N=32	Patients undergoing endoscopic sinus surgery.	Hospital in Germany.	Controlled hypotension (MAP 65-75mmHg) using sodium nitroprusside	Blood loss (mL) Mean (SD)	278 (528)	245 (440)	NS	
Other surgical procedures										
Kop et al. (2009)	Level II *Good*	N=85	Patients (<60 years, ASA I and II) undergoing bilateral breast reduction surgery.	Hospital in the Netherlands.	Controlled hypotension (MAP >50mmHg) using sodium nitroprusside	Blood loss (mL) Mean (range)	316 (133–560)	598 (250–1335)	<0.001	See meta-analysis
Sood et al. (1987)	Level II *Fair*	N=18	Patients undergoing elective, proximal, lienorenal shunts for portal hypertension.	Hospital in India.	Controlled hypotension (SBP 90-95mmHg) using sodium nitroprusside	Blood loss (mL) Mean (SD)	517 (220)	1286 (523)	<0.01	

Abbreviations: ASA, American Society of Anaesthesiologists; BP, blood pressure; MAP, mean arterial pressure; NR, not reported; NS, not statistically significant; SD, standard deviation.

[a] Three publications (Boldt et al., Piper et al. and Suttner et al.) were conducted at the same institution. However, based on information in the publications, it is not possible to determine if there was an overlap in the study populations. Consequently, lack of independence should be considered during the interpretation of the results from these three studies.

Meta-analysis of the effect of deliberate induced hypotension on blood loss during surgery



Meta-analysis shows that patients with induced hypotension on average lose 460mL less blood. Test of heterogeneity showed that the volume of blood loss varied significantly between surgical procedures.

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on mortality?		Evidence table ref*: POQ3.I5.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study of good quality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No deaths occurred in either patient group.	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
This study was conducted in patients undergoing prostatectomy, as such, the generalisability of the evidence would be limited to patients undergoing this surgical procedure.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The RCT was conducted in Canada, as such, the evidence is likely applicable to Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One good quality RCT
2. Consistency	NA	Not applicable
3. Clinical impact	D	No deaths occurred in either patient group.
4. Generalisability	C	This study was conducted in patients undergoing prostatectomy, as such, the evidence would be most generalisable to patients undergoing this surgical procedure.
5. Applicability	B	This study was conducted in Canada, as such, the evidence is likely applicable to Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on mortality is uncertain.

POQ3.I5.P4 Characteristics and results of studies examining the effect of deliberate induced hypotension on mortality

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
O'Connor et al. (2006)	Level II *Good*	N=99	Patients with adenocarcinoma of the prostate to undergo radical retropubic prostatectomy.	Medical Institution in Canada.	Hypotension induced using epidural and ropivacaine (MAP 55-60mmHg)	Serious adverse events	0	0	NA	Includes death, myocardial infarction, stroke, renal impairment, DVT, PE

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism.

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on morbidity?		Evidence table ref*: POQ3.I5.P5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies: 2 good quality RCTs, 1 fair quality RCT.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Several different morbidity outcomes were examined. None of the RCTs observed a significant difference between treatment groups for the morbidity outcomes examined (serious adverse events, incidence of DVT and PE).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant difference between patient groups	A	Very large
	B	Substantial
	C	Moderate
	D	No difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The generalisability of the evidence is likely limited to the morbidity outcome in the specific surgical patient populations examined by the respective studies.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The RCTs were conducted in Germany, Canada and Sweden. As such the findings from these studies are likely applicable to Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Clinical/Consumer Reference Group noted that the study by Fredin et al. was conducted in 1983; as such differences in surgical practices and patient management, relating to pulmonary embolism, may reduce the applicability of the study.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	Two RCTs of good quality and one RCT of fair quality.
2. Consistency	B	Several different morbidity outcomes were examined. None of the studies observed a significant effect of induced hypotension on the incidence of morbid events.
3. Clinical impact	D	No significant difference between patient groups. Underpowered.
4. Generalisability	C	The generalisability of the evidence is likely limited to the morbidity outcome in the specific surgical patient populations examined by the respective studies.
5. Applicability	C	The RCTs were conducted in Germany, Canada and Sweden. As such the findings from these studies are likely applicable to Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on morbidity is uncertain.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; RCT, randomised clinical trial.

POQ3.I5.P5 Characteristics and results of studies examining the effect of deliberate induced hypotension on morbidity

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
O'Connor et al. (2006)	Level II *Good*	N=99	Patients with adenocarcinoma of the prostate to undergo radical retropubic prostatectomy.	Medical Institution in Canada.	Hypotension induced using epidural and ropivacaine (MAP 55-60mmHg)	Serious adverse events	0	0	NA	Includes death, myocardial infarction, stroke, renal impairment, DVT, PE
Fredin et al. (1984)	Level II *Fair*	N=57	Patients undergoing total hip arthroplasty.	Hospital in Sweden.	Controlled hypotension (SBP 70-80mmHg) using sodium nitroprusside	Incidence of DVT n/N (%)	11/24 (46%)	10/26 (38%)	NS	–
						Incidence of PE n/N (%)	6/26 (26%)	1/28 (4%)	NS	–

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; NR, not reported; NS, not statistically significant; PE, pulmonary embolism.

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on quality of life?		Evidence table ref*: POQ3.I5.P6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies identified in literature search	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on quality of life is unknown.

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on haemoglobin concentration?			Evidence table ref*: POQ3.I5.S1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Two level II studies: both of fair quality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
The findings of the two RCTs differed. Piper et al. examined patients undergoing prostatectomy and found that patients with induced hypotension had significantly higher haemoglobin concentration during and after surgery. Krakaya et al. examined patients undergoing hip arthroplasty and reported that there was no significant difference in haemoglobin concentration between patient groups.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Conflicting evidence	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The effects observed are likely generalisable to patients undergoing the surgical procedures examined in each of the respective studies.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Piper et al. was conducted in Germany, as such the findings are likely applicable in the Australian context. Karakaya et al. was conducted in Turkey. Additional information on the healthcare system would allow an assessment of the applicability of findings.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Clinical/Consumer Reference Group noted that the measure of haemoglobin concentration was a surrogate for blood loss. Please see POQ3.I5.P3 for the evidence on blood loss.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two RCTs of fair quality.
2. Consistency	D	The studies had inconsistent findings.
3. Clinical impact	D	Only one study observed a significant effect. The haemoglobin concentrations in patients with induced hypotension appeared to be ~1.5g/dL higher, compared to patients with normotension.
4. Generalisability	C	The evidence is likely generalisable to patients undergoing the surgical procedures examined in each of the respective studies.
5. Applicability	C	The study by Piper et al. was conducted in Germany, as such the evidence is probably relevant in Australia. In contrast, the study by Karakaya et al. was conducted in Turkey, which may limit the applicability of the evidence.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on haemoglobin concentration is uncertain.

POQ3.I5.S1 Characteristics and results of studies examining the effect of deliberate induced hypotension on haemoglobin concentration

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Piper et al. (2002)	Level II *Fair*	N=30	Patients undergoing elective radical prostatectomy (ASA class II and III only).	Hospital in Germany.	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Postoperative haemoglobin concentration	Significantly higher in intervention group (see figure below)		P<0.05	–
Karakaya et al. (1999)	Level II Fair	N=20	ASA class I and II patients undergoing primary total hip arthroplasty	Medical Institution in Turkey.	Nitroglycerine induced hypotension (MAP 60-65mmhg)	Haemoglobin concentrations (g/dL)	After intubation: 11.6 (0.4)	11.9 (0.8)	NS	
							After operation: 9.2 (0.19)	9.7 (0.2)		
							After 5 days: 10.2 (0.3)	10.3 (0.5)		

Abbreviations: ASA, American Society of Anaesthesiologists; MAP, mean arterial pressure; NS, not statistically significant.

Figure from Piper et al. 2002.

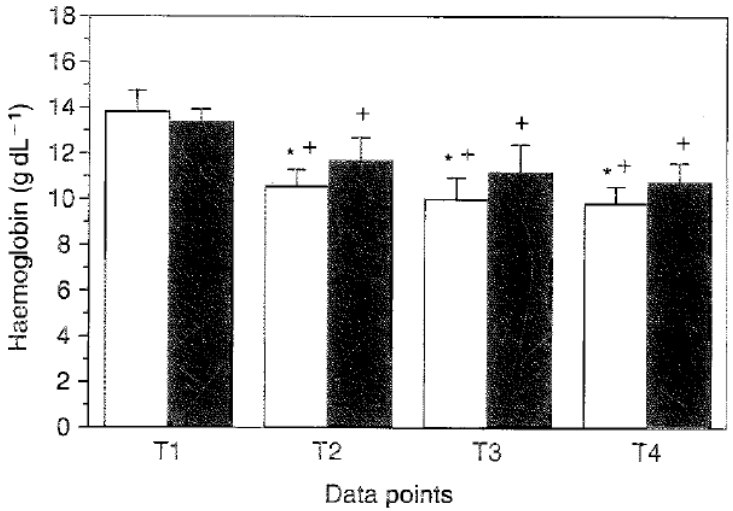


Figure 1.
Changes in haemoglobin concentration with time. T1: after induction of general anaesthesia; T2: at the end of surgery; T3: 2 h postoperatively; T4: 24 h postoperatively. Data are the mean ± SD. $^{*}P < 0.05$ *different versus the other group.* $^{+}P < 0.05$ *different versus the baseline.* □*: Control group;* ■*: hypotension group.*

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on coagulation status?		Evidence table ref*: POQ3.I5.S3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One good quality RCT.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant difference in coagulation data (aPTT, AT III, fibrinogen, platelet count) were observed between patient groups	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The generalisability of the evidence is likely limited to patients undergoing prostatectomy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Germany, as such the findings are likely applicable to Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Clinical/Consumer Reference Group noted that the study by Fredin et al. was conducted in 1983, as such differences in surgical practices and patient management, relating to pulmonary embolism, may reduce the applicability of the study.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One RCT of good quality
2. Consistency	NA	Only one included study.
3. Clinical impact	D	No significant difference between patient groups.
4. Generalisability	C	The generalisability of the evidence is likely to patients undergoing prostatectomy.
5. Applicability	C	The study was conducted in Germany, as such the findings are likely applicable to Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on coagulation status is uncertain.

Abbreviations: aPTT, activated partial thromboplastin time; AT, antithrombin III; RCT, randomised clinical trial.

POQ3.I5.S3 Characteristics and results of studies examining the effect of deliberate induced hypotension on coagulation status

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Boldt et al. (1999)	Level II *Good*	N=40	Patients under the age of 75 years undergoing retropubic radical prostatectomy with bilateral pelvic lymphadenectomy.	Hospital in Germany.	Controlled hypotension (MAP ~50mmHg) using sodium nitroprusside	Coagulation status	Pre-op: 34.1 (2.7) Post-op: 42.3 (5.4)	Pre-op: 34.3 (2.3) Post-op: 52.2 (12.1)	NS	–
							Pre-op: 78.7 (5.5) Post-op: 58.7 (4.3)	Pre-op: 81.5 (7.8) Post-op: 60.1 (12.1)	NS	
							Pre-op: 308 (39) Post-op: 181 (37)	Pre-op: 318 (44) Post-op: 145 (22)	NS	
							Pre-op: 209 (30) Post-op: 166 (35)	Pre-op: 221 (36) Post-op: 119 (33)	NS	

Abbreviations: aPTT, activated partial thromboplastin time; AT, antithrombin III; NS, not statistically significant.

Key question(s): In patients undergoing surgery, what is the effect of deliberate induced hypotension on hospital length of stay?		Evidence table ref*: POQ3.I5.S5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level II study, of good quality was identified. The study examined patients undergoing prostatectomy.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no significant difference in the number of patients who stayed in hospital for more than 5 days between treatment groups.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The effects are likely generalisable to only patients undergoing prostatectomy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study was conducted in Canada, as such the findings are likely applicable in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The CRG noted that the use of epidural in the study by O'Connor may have affected the hospital length of stay (eg, due to reduced mobility). Consequently, the findings may not be relevant for the purposes of this review.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	One RCT of good quality.
2. Consistency	NA	Not applicable
3. Clinical impact	D	There was no significant difference between patient groups.
4. Generalisability	C	The effects are likely generalisable to only patients undergoing prostatectomy.
5. Applicability	B	This study was conducted in Canada, as such the findings are likely applicable in the Australian context.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on length of hospital stay is uncertain.

POQ3.I5.S5 Characteristics and results of studies examining the effect of deliberate induced hypotension on hospital length of stay

Study	Level of evidence *Quality*	No. of trials (N)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
O'Connor et al. (2006)	Level II *Good*	N=99	Patients with adenocarcinoma of the prostate to undergo radical retropubic prostatectomy.	Medical Institution in Canada.	Hypotension induced using epidural and ropivacaine (MAP 55-60mmHg)	Hospital stay > 5 days n/N (%)	24/49 (49%)	34/50 (68%)	P=0.055	–

Abbreviations: MAP, mean arterial pressure.

Recommendation(s) for deliberate induced hypotension

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In patients undergoing radical prostatectomy or major joint replacement, if substantial blood loss is anticipated, deliberate induced hypotension (mean arterial blood pressure 50–60 mmHg) should be considered, balancing the risk of blood loss and the preservation of vital organ perfusion.	C	PO3.I5.P1, PO3.I5.P2, PO3.I5.P3

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?	YES	NO

Intervention 6 – Prevention of hypothermia

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on transfusion incidence?		Evidence table ref*: POQ3.I6.P1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level I studies: 1 good quality (Rajagopalan et al. 2008), 1 fair quality (Scott et al. 2006). Publication bias was assessed in the review by Rajagopalan et al. and found to be low. One level II study: One RCT was identified and considered to be of fair quality (Yau et al. 1992).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Test of heterogeneity across the 10 RCTs in the review by Rajagopalan et al. was not significant (P=0.25). Both Rajagopalan et al. and Scott et al. observed a significant reduction in transfusion incidence. It is important note that two of the three studies included by Scott et al. for this outcome, were also included in the review by Rajagopalan et al. The level II study showed a non-significant effect. The study had a small sample size (N=20) and examined the incidence of red blood cell transfusion rather than blood transfusion, these factors may have contributed to the inconsistent finding.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Meta-analysis of the level I and II studies revealed a risk ratio of 0.78 (0.63, 0.96), P=0.021). This indicates that the overall incidence of transfusion is 22% lower in patients when hypothermia prevention strategies are used.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The systematic reviews by Rajagopalan et al. and Scott et al. included studies which examined patients undergoing hip surgery, cardiac surgery, abdominal and colorectal surgery. As such, the evidence is likely generalisable to a broad range of surgical procedures.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies included in the systematic review by Rajagopalan et al. were mainly conducted in Europe and the US, while the RCT was conducted in Canada. As such, the evidence is likely applicable in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Clinical/Consumer Reference Group suggested caution in the interpretation of the results from the study by Yau et al. due to the method of hypothermia prevention used (warming of systemic perfusion) and the small sample size (N=20).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	1 good and 1 fair systematic review that comprised 11 RCTs from a range of surgical procedures
2. Consistency	B	The results from the studies were largely consistent.
3. Clinical impact	B	Meta-analysis of all the studies identified revealed a significant reduction in transfusion incidence, with the use of hypothermia prevention strategies (RR 0.78, 95%CI 0.63, 0.93)
4. Generalisability	B	The studies included patients from a variety of surgical procedures and should be generalisable to a broad patient population.
5. Applicability	B	Studies were conducted in countries with a comparable healthcare system to Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

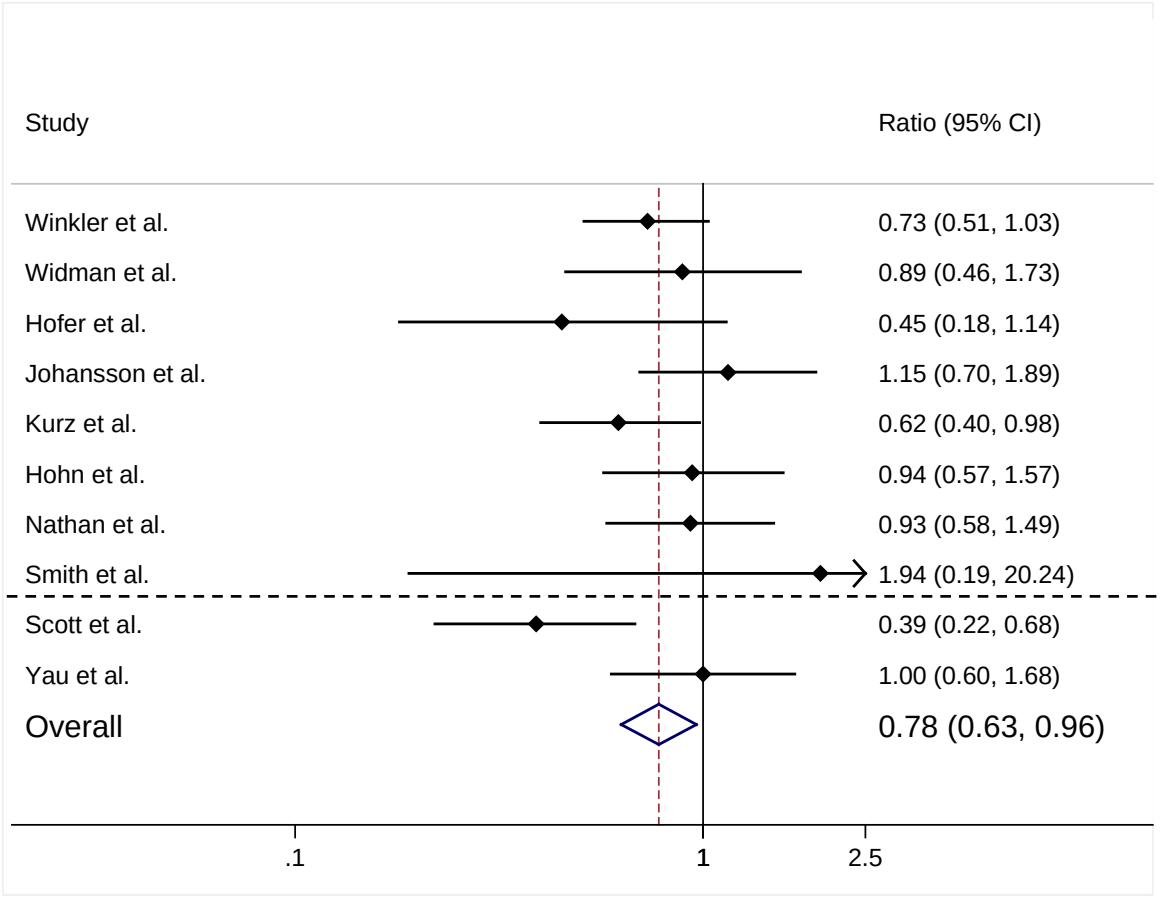
In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia reduces the incidence of transfusion.

POQ3.I6.P1 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on transfusion incidence

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Rajagopalan et al. (2008)	Level I *Good*	10 (N=895)	Patients undergoing any surgical procedure	NR	Maintenance of normothermia, compared to patients with non-induced mild hypothermia	Ratio for need of blood transfusion (intervention vs control)	0.78 (0.63, 0.97)		P=0.027	Search date: 1996 to Oct 2006 Test of heterogeneity (P=0.25). Low publication bias observed.
Scott et al. (2006)	Level I *Fair*	3 (N=250)[a]	Patients undergoing any surgical procedure (except cardiac procedures) under regional or general anaesthesia.	NR	Maintenance of normothermia, compared to patients with non-induced hypothermia	Ratio for need of blood transfusion (intervention vs control)	0.39 (0.22, 0.68)		NR	Search date: 1948 to May 2003 No test of heterogeneity or bias conducted.
Yau et al. (1992)	Level II *Fair*	N=20	Patients undergoing isolated primary CABG.	Hospital in Canada	Warm systemic perfusion	Red blood cell transfusion incidence n/N (%)	6/8 (75)	9/12 (75)	NS	–

Abbreviations: CABG, coronary artery bypass graft; NR, not reported; NS, not statistically significant; SD, standard deviation.
[a] Two of the three studies identified by Scott et al. were also included in the review by Rajagopalan et al.

Meta-analysis of effect of the prevention of hypothermia on transfusion incidence



Studies included in Rajagopalan et al. (excluding those included in Scott et al.)

Meta-analysis (random effects model used) of the two Level I studies and one RCTs revealed a risk ratio of 0.78 (95% CI 0.63, 0.96), P=0.021. This indicates that the incidence of transfusion was 22% lower in patients when hypothermia prevention strategies were used.

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on transfusion volume?		Evidence table ref*: POQ3.I6.P2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study: 1 poor quality review (Mahoney et al. 1999) Two level II studies: 1 fair quality (Zhao et al. 2005), 1 poor quality (Jeong et al. 2008)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
No test of heterogeneity was conducted by the systematic review. Although a significant reduction in transfusion volume was observed in the systematic review, the two other RCTs (from South Korea and China) failed to detect a significant effect. This may be due to differences in the surgical procedures examined, or the small sample sizes of the RCTs identified (N=40 each).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The systematic review reported that the prevention of hypothermia significantly reduced transfusion volume of red blood cells (0.12 Units vs 1.17 Units, P<0.05). The Level II studies reported that the prevention of hypothermia actually increased transfusion volume, although the difference was not statistically significant.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The systematic review identified five studies which examined RBC transfusion, this comprised patients from any surgical procedure. As such, the results is likely generalisable to a general surgical patient population. The two RCTs identified examined patients undergoing CABG and abdominal surgery; consequently, the evidence is likely limited to patients undergoing such surgical procedures.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The systematic review included studies mainly conducted in western countries, and as such, the evidence is likely applicable in Australia. In contrast, the two RCTs were conducted in Korea and China. Consequently, the applicability of the evidence may be more limited.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The five studies identified in the systematic review included one non-randomised study (N=262), which could potentially affect the accuracy of the pooled effect estimate.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	1 poor quality systematic review. 1 poor and 1 fair quality RCT.
2. Consistency	C	Significant effect reported in systematic review, but not in 2 other RCTs. Differences in study design, sample size and population make it difficult to rationalise the inconsistency.
3. Clinical impact	D	A significant difference in transfusion volume was observed in the systematic review. However, the inclusion of a non-randomised study diminished confidence in the findings of the study.
4. Generalisability	C	The studies identified comprise patients undergoing a variety of surgery.
5. Applicability	C	The systematic review comprised studies conducted mostly in western countries, which are similarly developed to Australia. As such, the evidence is likely applicable in the Australian context. The two RCTs were conducted in South Korea and China, which may limit the applicability of the findings from those studies.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia may reduce the volume of transfusion.

Abbreviations: CABG, coronary artery bypass graft; RBC, red blood cell.

POQ3.I6.P2 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on transfusion volume

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Mahoney et al. (1999)	Level I *Poor*	5 (N=859) [a]	Patients undergoing any surgical procedure	NR	Maintenance of normothermia, compared to patients with non-induced hypothermia	Units of RBC transfused Mean (SD)	0.12 (0.02)	1.17 (0.09)	P<0.05	Search Date: 1989 to 1997 No test of heterogeneity or bias conducted.
Jeong et al. (2008)	Level II *Poor*	N=40	Patients undergoing isolated off-pump coronary artery bypass surgery.	Hospital in South Korea	Warming of all intravenous fluids	Blood transfused (mL) Mean (SD)	400.5 (622.8)	365.0 (437.1)	NS	–
Zhao et al. (2005)	Level II *Fair*	N=40	ASA class I and II patients undergoing abdominal surgery lasting at least 2 hours.	Hospital in China	Warming from a forced-air blanket and warming of all intravenous fluids.	RBC transfused (Units) Mean (SD)	2.6 (2.5)	1.6 (2.4)	NS	–
						Plasma transfused (mL) Mean (SD)	220 (460)	240 (480)	NS	

Abbreviations: ASA, American Society of Anaesthesiologists; CABG, coronary artery bypass graft; CI, confidence interval; NR, not reported; NS, not statistically significant; RBC, red blood cells; SD, standard deviation.
[a] Includes one non-randomised controlled trial (N=262).

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on blood loss?			Evidence table ref*: POQ3.I6.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
One level I study: The systematic review by Rajagopalan et al. (2008) was considered to be of good quality. Publication bias was assessed using a funnel plot and determined to be low. Two level II studies: 2 RCTs of fair quality (Zhao et al. 2005; Yau et al. 1992).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Test of heterogeneity across the 14 RCTs in the review by Rajagopalan et al. was significant (P<0.001). Accordingly, a random effects model was used in the meta-analysis. The meta-analysis conducted by Rajagopalan et al. showed a significant reduction in blood loss. None of the level II studies showed a significant effect on blood loss. The variability of the observed effects may be due to the different hypothermia prevention methods employed, and the different surgical procedures examined by the different studies.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
A meta-analysis of the two Level II studies, together with the 14 studies included in the systematic review by Rajagopalan 2008 was conducted. The meta-analysis estimate indicates that the use of hypothermia prevention strategies resulted in a 14% lower average blood loss in patients as compared to patients where hypothermia was not prevented (Ratio: 0.86 (95%CI 0.76, 0.98), P=0.021).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The level I and II studies identified include studies which examined patients undergoing a variety of surgical procedures. As such, the results are likely to be generalisable to a broad range of surgical patient populations.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The studies included in the systematic review by Rajagopalan et al. were mainly conducted in Europe and the US, consequently, the findings are likely applicable in the Australian context. One of the RCTs was conducted in Canada, and is also likely applicable in the Australian context. The other RCT was conducted in China; as such, the evidence from these studies may not be as applicable in Australia.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Clinical/Consumer Reference Group suggested caution in the interpretation of the results from the study by Yau et al. due to the method of hypothermia prevention used (warming of systemic perfusion) and the small sample size (N=20).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	1 good quality systematic review. 2 fair quality RCTs.
2. Consistency	C	Some variability between studies was observed, this may be due to the different hypothermia prevention methods used and different surgical procedures examined.
3. Clinical impact	B	A meta-analysis of the level I and II studies showed that blood loss was reduced by 14% when hypothermia was prevented (Ratio: 0.86 (95%CI 0.76, 0.98)).
4. Generalisability	B	The level I and II studies identified include studies which examined patients undergoing a variety of surgical procedures.
5. Applicability	B	The systematic review included studies mainly conducted in Europe and the US, as such the evidence is likely applicable in Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

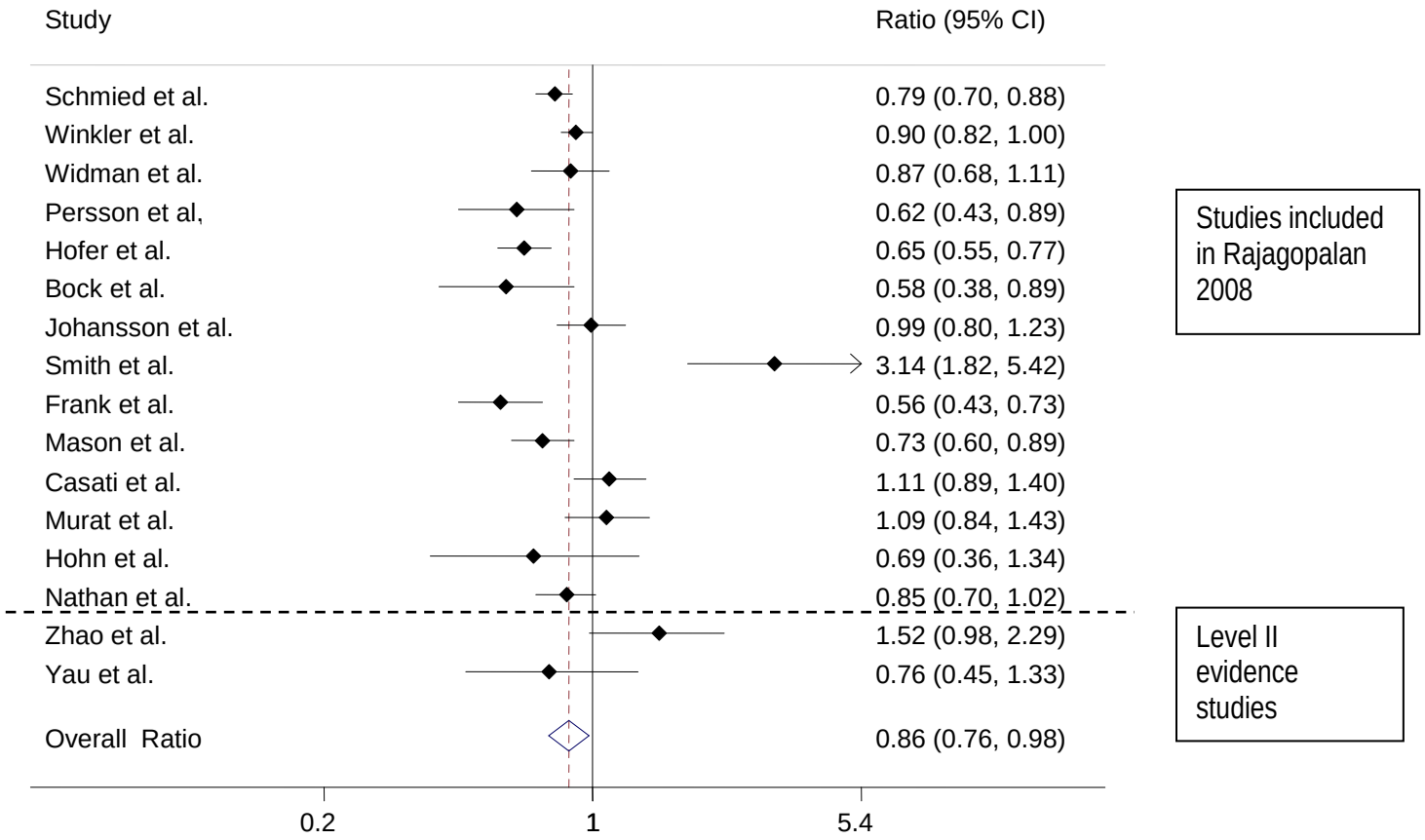
In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia reduces blood loss.

POQ3.I6.P3 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on blood loss

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Rajagopalan et al. (2008)	Level I *Good*	14 (N=1249)	Patients undergoing any surgical procedure	NR	Maintainence of normothermia, compared to patients with non-induced mild hypothermia	Ratio of blood loss (intervention vs control)	0.84 (95%CI 0.74, 0.96)		0.009	Search date: 1996 to Oct 2006 Test of heterogeneity: P<0.001 Low publication observed
Zhao et al. (2005)	Level II *Fair*	N=40	ASA class I and II patients undergoing abdominal surgery lasting at least 2 hours.	Hospital in China	Warming from a forced-air blanket and warming of all intravenous fluids.	Blood loss (mL) Mean (SD)	639 (441)	421 (249)	NS	–
Yau et al. (1992)	Level II *Fair*	N=20	Patients undergoing isolated primary CABG.	Hospital in Canada	Warm systemic perfusion	Blood loss (mL) Mean (SD)	949 (427)	1253 (796)	NS	–

Abbreviations: ASA, American Society of Anaesthesiologists; CABG, coronary artery bypass graft; CI, confidence interval; NR, not reported; NS, not statistically significant; SD, standard deviation.
Note: To clarify the effect of hypothermia prevention on blood loss, a meta-analysis of the two Level II studies, together with the 14 studies included in the systematic review by Rajagopalan 2008 was conducted.

Meta-analysis of ratio of blood loss (Hypothermia prevention : No prevention)



Treatment effect is expressed as a ratio of the mean blood loss between treatment groups rather than a difference in mean as this allows a more intuitive comparison of studies examining different surgical procedures with varying volumes of blood loss.

The meta-analysis estimate (random effects model) indicates that the use of hypothermia prevention strategies resulted in a 14% lower average blood loss in patients as compared to patients where hypothermia was not prevented (Ratio: 0.86 (95%CI 0.75, 0.98), P=0.021).

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on mortality?			Evidence table ref*: POQ3.I6.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Only one level I study, of poor quality, was identified (Mahoney et al. 1999).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
No test of heterogeneity was reported in the systematic review. The systematic review identified two studies which reported on transfusion dose, one of which was a non-randomised controlled trial. The pooled effect estimates from the two studies showed a significant reduction in mortality rate when hypothermia was prevented (2.7% vs 6.01%, P<0.05). However, data retrieved from the only the RCT did not show a significant effect of hypothermia prevention on mortality (1.3% vs 1.4%, P=0.91).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The systematic review found that the prevention of hypothermia significantly reduced mortality in patients undergoing surgery (2.7% vs 6.01%, P<0.05), however, the pooled effect was derived from two studies, of which, only one was randomised. Data from only the randomised study showed hypothermia prevention did not have an effect on mortality rate (1.3% vs 1.4%, P=0.91).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The systematic review included two studies that reported mortality rates in patients undergoing abdominal, vascular and thoracic surgery. As such the evidence is likely generalisable to patients undergoing such surgical procedures.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The studies included in the systematic review were conducted in the US, as such the findings are probably applicable in the Australian context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The systematic review by Mahoney et al. included one RCT and one non-randomised study to derive the mortality rate estimate.
Using only the data from the randomised study showed that prevention of hypothermia did not have an effect on mortality rate (1.3% vs 1.4%, P=0.91).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One level 1 study, of poor quality. Only two of the studies identified in the review reported mortality rates.
2. Consistency	NA	Only 1 systematic review was identified, no test of heterogeneity was reported.
3. Clinical impact	D	There was no evidence for an effect on mortality rate.
4. Generalisability	B	The studies identified included patients undergoing abdominal vascular and thoracic surgery. As such, the evidence is likely relevant to patients undergoing such procedures.
5. Applicability	C	Studies identified were conducted in the US, as such, the evidence is probably applicable in Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on mortality is uncertain.

POQ3.I6.P4 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on mortality

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Mahoney et al. (1999)	Level I *Poor*	2 (N=562) [a]	Patients undergoing any surgical procedure	NR	Maintenance of normothermia, compared to patients with non-induced hypothermia	Mortality rate Pooled mean % (SD)	Pooled Incidence (RCT & non-RCT)		P<0.05	Search Date: 1989 to 1997 No test of heterogeneity or bias conducted
							2.70%	6.01%		
							Incidence from RCT (N=300)		P=0.91	
							2/158 (1.3%)	2/142 (1.4%)		

Abbreviations: NR, not reported; SD, standard deviation.

[a] Includes an RCT (N=300) and a non-randomised controlled trial (N=262).

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on morbidity?		Evidence table ref*: POQ3.I6.P5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Two level I studies: 1 of fair quality (Scott et al.) and 1 of poor quality (Mahoney et al.) Two level II studies: 1 good quality RCT (Melling et al.), 1 fair quality RCT (Kim et al.). Note: The systematic review by Mahoney et al. (1999) included two studies which reported on morbidity outcomes, one of the studies was also included in the more recent review by Scott et al. (2006).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Several different morbidity outcomes were examined. The prevention of hypothermia was found to significantly reduce the incidence of outcomes such as morbid cardiac events and wound infections. The studies by Scott et al. and Kim et al. failed to find a significant effect of the intervention on pain.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Meta-analysis by Scott et al. showed that primary complication (morbid cardiac events, wound infection) were reduced by 63% in patients where hypothermia was prevented (P<0.00001).Mahoney et al. also reported significantly lower rates of myocardial infarction when hypothermia was prevented in patients (2.3% vs 4.1%, P<0.05). The study by Melling et al. also showed that wound infection was reduced (5% vs 14%, P=0.001).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The level I and II studies identified examined patients undergoing a variety of surgical procedures. As such, the evidence is likely generalisable to a broad range of surgical patient populations.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The systematic reviews and the RCT by Melling et al. were conducted in countries in Europe, US and the UK. As such, the evidence is likely applicable in the Australian context. The study by Kim et al. was conducted in a military hospital in South Korea, as such, the findings of that study are probably not applicable.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The systematic review by Mahoney et al. included one non-randomised study (N=262), which may have affected the accuracy and reliability of the effect estimate.
The Clinical/Consumer Reference Group (CRG) suggested caution in the interpretation of the study by Melling et al. as it included operations with short durations and warming was done only preoperatively.
The CRG also noted that the morbid cardiac events, as reported by Scott et al., did not include the morbid outcomes of interest for this review, but rather haemodynamic changes (eg. tachycardia and hypotension)

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	2 systematic reviews comprising 8 studies in total. In addition to 1 good quality and 1 fair quality RCT.
2. Consistency	B	The systematic review found that hypothermia prevention significantly reduced the incidence of cardiac events and wound infection. However, this was derived from data of two studies only.
3. Clinical impact	C	Meta-analysis showed that primary complications (morbid cardiac events, wound infections) were reduced by 63% in patients where hypothermia was prevented
4. Generalisability	B	The studies identified included a patients undergoing any surgery, as such, the evidence is likely generalisable to patients undergoing a range of procedures.
5. Applicability	B	Except for the RCT by Kim et al., which was conducted in a military hospital in South Korea, the evidence from the other studies is probably applicable in Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia reduces the incidence of wound infection.

POQ3.I6.P5 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on morbidity

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Scott et al. (2006)	Level I *Fair*	7 (N=1061)	Patients undergoing any surgical procedure (except cardiac procedures) under regional or general anaesthesia.	NR	Maintenance of normothermia, compared to patients with non-induced hypothermia	All primary complications	0.37 (0.27, 0.51)		<0.00001	Search date: 1948 to May 2003 No test of heterogeneity or bias conducted
		2 (N=287)				Morbid cardiac events [a] RR (95%CI)	0.34 (0.20, 0.57)		NR	
		2 (N=284)				Wound infection RR (95%CI)	0.26 (0.12, 0.58)		NR	
		3 (N=131)				Pain	No significant difference in pain between treatment groups		NS	
Mahoney et al. (1999)	Level I *Poor*	2 (N=562) [b]	Patients undergoing any surgical procedure	NR	Maintenance of normothermia, compared to patients with non-induced hypothermia	Myocardial infarction Pooled mean % (SD)	2.3% (0.88)	4.1% (1.34)	P<0.05	Search Date: 1989 to 1997 No test of heterogeneity or bias conducted
Melling et al. (2001)	Level II *Good*	N=421	Patients having clean surgery (e.g. breast, varicose vein, or hernia), that would result in a scar longer than 3 cm.	Hospital in UK	Preoperative warming	Wound infection n/N (%)	13/277 (5)	19/139 (14)	P=0.001	–
Kim et al. (2009)	Level II *Fair*	N=50	ASA I or II patients undergoing arthroscopic shoulder surgery.	Military hospital in South Korea	Use of warm irrigation fluid	Pain measured using the VAS score	5.0 (1.7)	4.9 (1.6)	P=0.927	–

Abbreviations: ASA, American Society of Anaesthesiologists; CI, confidence interval; NR, not reported; NS, not statistically significant; RR, relative risk; SD, standard deviation; VAS, visual analogue score.

[a] Includes hypertension, tachycardia, angina, cardiac arrest or myocardial infarction recoded on an electrocardiograph monitor.

[b] Includes one non-randomised controlled trial.

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on quality of life?		Evidence table ref*: POQ3.I6.P6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies identified in literature search	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	There were no studies that reported data on quality of life.
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on quality of life is unknown.

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on haemoglobin concentration?			Evidence table ref*: POQ3.I6.S1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Two level II studies: both of fair quality (Kim et al. and Yau et al.)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Both level II studies did not observe a significant effect of hypothermia prevention on haemoglobin concentration.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No significant effect was reported.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	No difference	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The RCT by Kim et al. was conducted in patients undergoing arthroscopic shoulder surgery, while Yau et al. examined patients undergoing CABG surgery. Generalisability of the findings is likely limited to patients undergoing the aforementioned surgical procedures.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study by Kim et al. was conducted in a military hospital in South Korea; accordingly, the evidence may not be applicable in the Australian context. The study by Yau et al. was conducted in a hospital in Canada, as such the findings in this study are likely applicable in Australia.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Clinical/Consumer Reference Group suggested caution in the interpretation of the results from the study by Yau et al. due to the method of hypothermia prevention used (warming of systemic perfusion) and the small sample size (N=20).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	2 Level II studies of fair quality.
2. Consistency	A	Both studies did not observe a significant effect of hypothermia prevention on haemoglobin levels.
3. Clinical impact	D	No significant effect observed.
4. Generalisability	C	Generalisability of the findings is likely limited to the two surgical procedures examined by the two RCTs identified.
5. Applicability	D	One RCT was conducted in a military hospital in South Korea, as such the evidence may not be applicable in Australia. In contrast, the other RCT was conducted in Canada, as such, the findings are probably applicable in Australia.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on haemoglobin concentration is uncertain.

Abbreviations: CABG, coronary artery bypass graft.

POQ3.I6.S1 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on haemoglobin concentration

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Kim et al. (2009)	Level II *Fair*	N=50	ASA I or II patients undergoing arthroscopic shoulder surgery.	Military hospital in South Korea	Use of warm irrigation fluid	Decrease in haemoglobin after surgery (g/dL) Mean (SD)	1.7 (0.7)	1.4 (0.6)	0.165	–
Yau et al. (1992)	Level II *Fair*	N=20	Patients undergoing isolated primary CABG.	Hospital in Canada	Warm systemic perfusion	Postoperative haemoglobin concentration	No significant difference between treatment groups		NR	–

Abbreviations: ASA, American Society of Anaesthesiologists; CABG, coronary artery bypass graft; CI, confidence interval; NR, not reported; standard deviation; VAS, visual analogue score.

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on hospital length of stay?		Evidence table ref*: POQ3.I6.S5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study: 1 systematic review of poor quality (Mahoney et al.) One level II study: 1 poor quality (Jeong et al.).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The review by Mahoney et al. found that the prevention of hypothermia in patients was associated with a significantly shorter hospital stay. Similarly Jeong et al. observed a shorter hospital stay in patients in the intervention group, however, the difference was not statistically significant (10.6 days vs 11.6 days).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
On average, the prevention of hypothermia was estimated to reduce hospital stay by 1 to 7.7 days.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The systematic review included patients undergoing any surgical procedure, as such the findings are likely relevant to the general surgical patient population. The RCT by Jeong et al.was conducted in patients undergoing cardiac surgery, as such, findings from this study is likely limited to patients in this surgical group.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The systematic review by Mahoney et al included studies mostly conducted in Europe and the US. Accordingly, the findings are likely applicable in the Australian context. The RCT by Jeong et al. were conducted in South Korea. As such, the applicability of the findings may be more limited.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The systematic review by Mahoney et al. included one non-randomised study (N=262), which may have affected the accuracy and reliability of the effect estimate.
The CRG noted that they did not consider length of hospital stay to be a clinically relevant outcome in assessing the effect of the prevention of hypothermia during surgery.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	1 poor quality systematic review. 1 good quality RCT.
2. Consistency	C	The studies showed that patients experienced shorter hospital stays when hypothermia was prevented. The extent of the effect may vary according to the surgical procedure examined.
3. Clinical impact	NA	This outcome was not considered to be a clinically relevant outcome for this intervention.
4. Generalisability	D	The studies identified in this review included patients undergoing a range of surgical procedure. As such, the evidence likely is generalisable to a broad range of surgical patients.
5. Applicability	C	The studies included in the systematic review were conducted in Europe and US, as such the evidence is likely applicable to Australia. However, the RCTs by Jeong et al. were conducted in South Kore,a as such the applicability of those studies may be more limited.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on length of hospital stay is uncertain.

POQ3.I6.S5 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on hospital length of stay

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Mahoney et al. (1999)	Level I *Poor*	3 (N=762) [a]	Patients undergoing any surgical procedure	NR	Maintenance of normothermia, compared to patients with non-induced hypothermia	No. of days in hospital Pooled mean (SD)	11.77 (0.10)	19.44 (0.16)	<0.05	Search Date: 1989 to 1997 No test of heterogeneity or bias
Jeong et al. (2008)	Level II *Poor*	N=40	Patients undergoing isolated off-pump coronary artery bypass surgery.	Hospital in South Korea	Warming of all intravenous fluids	No of days in hospital Mean (SD)	10.6 (2.2)	11.6 (2.7)	NS	–

Abbreviations: NS, not statistically significant; NR, not reported; SD, standard deviation.
[a] Includes one non-randomised controlled trial.

Key question(s): In patients undergoing surgery, what is the effect of the prevention of hypothermia on length of ICU stay?		Evidence table ref*: POQ3.I6.S6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One level I study: 1 systematic review of poor quality (Mahoney et al.) One level II studies: 1 poor quality (Jeong et al.).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
All studies observed shorter stays in the ICU for patients when hypothermia was prevented. However, the difference was only significant in the review by Mahoney et al. The small sample size in the study by Jeong et al. may have reduced study power to detect a significant difference between the treatment groups.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The review by Mahoney et al. estimated that hypothermia prevention strategies during surgery reduced ICU stay by an average of 4.4 hours.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The systematic review by Mahoney et al. included patients undergoing any surgical procedure; as such the findings are likely relevant to the general surgical patient population. The RCT by Jeong et al.was conducted in patients undergoing cardiac surgery. As such, findings from this study is likely limited to patients in this surgical group.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The systematic review by Mahoney et al. included studies mostly conducted in Europe and the US, as such, the findings are likely applicable in the Australian context. The RCT by Jeong et al. was conducted in South Korea. As such, the applicability of the findings may be more limited.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The systematic review by Mahoney et al. included one non-randomised study (N=262), which may have affected the accuracy and reliability of the effect estimate.
The CRG noted that they did not consider ICU stay to be a clinically relevant outcome in assessing the effect of the prevention of hypothermia during surgery.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	1 systematic review of fair quality, 1 RCT of poor quality.
2. Consistency	C	Patients with hypothermia prevention experienced shorter ICU stays. However, this effect was not statistically significance in one of the RCTs.
3. Clinical impact	N/A	This outcome was not considered to be a clinically relevant outcome for this intervention.
4. Generalisability	D	The systematic review examined patients undergoing a range of surgical procedures, while the RCT examined cardiac surgery patients.
5. Applicability	C	Most of the data were from studies conducted in similarly developed countries like Australia. However, differences in the healthcare and hospital system may affect the applicability of the evidence.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on length of ICU stay is uncertain.

POQ3.I6.S6 Characteristics and results of studies examining the effect of the prevention of hypothermia during surgery on ICU stay

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Mahoney et al. (1999)	Level I *Poor*	2 (N=462) [a]	Patients undergoing any surgical procedure	NR	Maintenance of normothermia, compared to patients with non-induced hypothermia	ICU stay (hours) Pooled mean (SD)	5.51 (0.09)	9.70 (0.17)	P<0.05	Search Date: 1989 to 1997 No test of heterogeneity and bias conducted
Jeong et al. (2008)	Level II *Poor*	N=40	Patients undergoing isolated off-pump coronary artery bypass surgery.	Hospital in South Korea	Warming of all intravenous fluids	ICU stay (hours) Mean (SD)	59.6 (19.6)	70.5 (17.8)	NS	–

Abbreviations: ICU, intensive care unit; NS, not statistically significant; NR, not reported; SD, standard deviation.
[a] Includes one non-randomised controlled trial.

Recommendation(s) for prevention of hypothermia

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In patients undergoing surgery, measures to prevent hypothermia should be used.	A	PO3.I6.P1, PO3.I6.P2, PO3.I6.P3, PO3.I6.P5

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Increased use of warming methods.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Equipment costs.		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Cost.		
What could help to facilitate implementation of the recommendation?	YES	NO
Targeted funding for warming devices.		

Intervention 7 – Point-of-care testing using thromboelastography

Key question(s): In patients undergoing surgery, what is the effect of TEG-based point-of-care testing on transfusion incidence?		Evidence table ref*: POQ3.I7.P1
1. Evidence base		
Level II evidence: Ak 2009 (fair quality; N=224); Avidan 2004 (fair quality; N=102); Shore-Lesserson 1999 (fair quality; N=105); Royston 2001 (poor quality; N=60) Level III evidence: Avidan 2004 (fair quality; N=159)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Meta-analyses of the Level II evidence were conducted herein using the results from Ak 2009, Avidan 2004, and Shore-Lesserson 1999[2]. The degree of heterogeneity between the trials was not significant for the transfusion incidence of PRBCs (P=0.36; I^2=1%), FFP (P=0.11; I^2=55%), or platelets (P=0.51; I^2=0%). The results from Royston 2001 are not significant, but agree in direction with the results of the meta-analysis. The Level III evidence from Avidan 2004 agrees with the meta-analysis results; however the results are only significant for PRBC transfusion, not FFP or platelet transfusion.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Meta-analysed results Incidence of PRBC transfusion – RR 0.84 (0.71, 1.00); P=0.05; N=431 Incidence of FFP transfusion – RR 0.52 (0.34, 0.81); P=0.003; N=431 Incidence of platelet transfusion – RR 0.56 (0.36, 0.87); P=0.01; N=431	A	Very large
	B	Substantial (FFP; PLT)
	C	Moderate
	D	Slight/Restricted (PRBC)
4. Generalisability		
The studies were all conducted in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The studies were conducted in Turkey (Ak 2009), UK (Avidan 2004; Royston 2001), and USA (Shore-Lesserson 1999).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Avidan 2004 provides Level II information for its RCT component and Level III if using the historical control arm.
Avidan 2004 included an algorithm with TEG and other tests.
For Royston 2001, the CRG assumed that red cells are inherent in blood component transfusion.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating			Description
	FFP	PRBC	PLT	
1. Evidence base	C	C	C	Several Level II and III studies with moderate risk of bias.
2. Consistency	C	C	C	Most studies consistent and inconsistency can be explained.
3. Clinical impact	B	D	B	Statistically significant and substantial clinical impact for FFP and PLT; not statistically significant for PRBC
4. Generalisability	B	B	B	All studies conducted in adults undergoing cardiac surgery
5. Applicability	B	B	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the use of thromboelastography may reduce the incidence of FFP and platelet transfusion; the effect on the incidence of RBC transfusion is uncertain.

Abbreviations: FFP, fresh frozen plasma; het, heterogeneity; PRBC, packed red blood cells; RR, risk ratio.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
[1] Royston 2001 was not included in the meta-analysis as the others reported the total units of blood components transfused but not the type of components transfused.
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.P1 Characteristics and results of studies examining the effect of point-of-care testing on transfusion incidence.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Ak (2009)	Level II *Fair*	N=224	Adults undergoing elective, first-time CABG with CPB.	Hospital in Turkey	TEG- based algorithm guided transfusion (comprising kaolin-activated (k) TEG and h-kTEG analyses) Comparator was clinician-directed transfusion[1]	Patients transfused with PRBC	52/114 (45.6%)	60/110 (54.5%)	P=0.181
						Patients transfused with FFP	19/114 (16.6%)	31/110 (28.1%)	P=0.038
						Patients transfused with platelets	17/114 (14.9%)	29/110 (26.3%)	P=0.033
Avidan (2004)	Level II (POC vs laboratory test) or Level III (POC vs clinical discretion) *Fair*	POC: N=51 Laboratory: N= 51 Clinical discretion: N=108	Adults undergoing elective, first-time CABG with CPB.	Hospital in UK	Algorithm based on near-patient haemostatic testing. POC devices used include ACT+/Junior, Hepcon HMS Hemostasis Management System, PFA-100 platelet function analyser; and two dual-channel TEG coagulation analysers used in parallel. Randomised comparator was algorithm using routine laboratory haemostatic tests and historical comparator was clinician discretion.	Patients transfused with PRBCs	POC: 34/51 (67%)	Laboratory: 35/51 (69%) Clinician discretion: 92/108 (85%)	Chi-square test: P=0.01 POC vs lab P=0.83 POC vs clinician P=0.02
						Patients transfused with FFP	POC: 2/51 (4%)	Laboratory: 0/51 (0%) Clinician discretion: 16/108 (15%)	Chi-square test: P=0.003 POC vs lab P=0.29 POC vs clinician P=0.07
						Patients transfused with platelets	POC: 2/51 (4%)	Laboratory: 1/51 (2%) Clinician discretion: 14/108 (13%)	Chi-square test: P=0.02 POC vs lab P=0.57 POC vs clinician P=0.10
Royston (2001)	Level II *Poor*	N=60	Adults undergoing cardiac surgery[2]	Hospital in UK	Heparinase-modified TEG-guided intraoperative algorithm. Comparator was transfusion guided by clinical criteria and laboratory-based tests	Patients transfused with blood components	5/30 (17%)	10/30 (33%)	P=0.15

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Shore-Lesserson (1999)	Level II *Fair*	N=105	Adults undergoing cardiac surgery with a moderate to high risk for requiring a transfusion	Hospital in USA	TEG-guided transfusion algorithm compared with standard laboratory-based transfusion therapy.	Patients transfused with allogeneic blood components (total)	22/53 (42%)	34/52 (65%)	P=0.01
						Patients transfused with packed RBCs (intraoperative)	17/53 (32%)	23/52 (44%)	P=0.2
						Patients transfused with packed RBCs (postoperative)	10/53 (19%)	16/52 (31%)	P=0.16
						Patients transfused with packed RBCs (total)	22/53 (42%)	31/52 (60%)	P=0.06
						Patients transfused with FFP (intraoperative)	3/53 (6%)	8/52 (44%)	P=0.12
						Patients transfused with FFP (postoperative)	2/53 (4%)	11/52 (21%)	P<0.05
						Patients transfused with FFP (total)	4/53 (8%)	16/52 (31%)	P<0.05
						Patients transfused with platelet concentrates (intraoperative)	5/53 (9%)	8/52 (15%)	P=0.4
						Patients transfused with platelet concentrates (postoperative)	3/53 (6%)	9/52 (17%)	P=0.06

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
						Patients transfused with platelet concentrates (total)	7/53 (13%)	15/52 (29%)	P<0.05

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; POC, point-of-care; PRBC, packed red blood cells; TEG, thromboelastography.

[1] Using criteria obtained from abnormal laboratory tests (PT, APTT and platelet count), absence of visible clots and presence of generalised oozing-type bleeding in the surgical field to determine blood product administration.

[2] Ten per cent of patients in each series had a heart transplantation and were taking aspirin and/or warfarin immediately before surgery. About 50% of the patients in each group had revascularisation and were also taking aspirin, and required multiple grafts with a bypass time estimated to be greater than 100 minutes. The remaining 40% of the patients were having the Ross procedure, multiple valve or valve and revascularisation surgery. No patients were having repeat operations and none received prophylactic aprotinin, epsilon aminocaproic acid or tranexamic acid.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on transfusion volume?				Evidence table ref*: POQ3.I7.P2
1. Evidence base				
Level II evidence: Ak 2009 (fair quality; N=224); Avidan 2004 (fair quality; N=102); Royston 2001 (poor quality; N=60); Shore-Lesserson 1999 (fair quality; N=105); Westbrook 2009 (fair quality; N=69) Level III evidence: Avidan 2004 (fair quality; N=159)	PRBC	FFP	PLT	
	A	A	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency				
The studies are consistent in finding no significant impact on volume of PRBC transfusion. Ak 2009 and Shore-Lesserson 1999 both found that the TEG-based clinical algorithm resulted in a significantly lower volume of FFP transfusion. Westbrook 2009 found no significant impact on volume of FFP transfusion. Ak 2009 found that the TEG algorithm resulted in a lower volume of platelet transfusion; whereas Shore-Lesserson 1999 and Westbrook 2009 found no significant difference between arms for this outcome. Royston 2001 found that TEG-based transfusion significantly reduced volume of blood components (FFP and platelets) transfused.	PRBC	FFP	PLT	
	A	A	A	All studies consistent
	B	B	B	Most studies consistent and inconsistency can be explained
	C	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	D	Evidence is inconsistent
	NA	NA	NA	Not applicable (one study only)
3. Clinical impact				
See Summary Table POQ3.17.P2	PRBC	FFP	PLT	
	A	A	A	Very large
	B	B	B	Substantial
	C	C	C	Moderate
	D	D	D	No difference
4. Generalisability				
The studies were all conducted in adults undergoing cardiac surgery.	PRBC	FFP	PLT	
	A	A	A	Evidence directly generalisable to target population
	B	B	B	Evidence directly generalisable to target population with some caveats
	C	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability				
The studies were conducted in Australia (Westbrook 2009), Turkey (Ak 2009), UK (Avidan 2004; Royston 2001), and USA (Shore-Lesserson 1999).	PRBC	FFP	PLT	
	A	A	A	Evidence directly applicable to Australian healthcare context
	B	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	D	Evidence not applicable to Australian healthcare context

Other factors

Generalisability rated as 'B' due to inclusion of Avidan 2004, which included TEG and other tests in their transfusion algorithm.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating			Description
	PRBC	FFP	PLT	
1. Evidence base	C	C	C	Five Level II studies with moderate risk of bias.
2. Consistency	A	B	C	Evidence is inconsistent.
3. Clinical impact	D	C	C	Moderate decrease in volume of FFPand PLT transfusion. No statistically significant impact on the volume of transfusion of PRBC.
4. Generalisability	B	B	B	Evidence not directly generalisable to the target population but could be sensibly applied.
5. Applicability	B	B	B	Evidence applicable to Australian healthcare context with few caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the use of thromboelastography may reduce the volume of FFP transfusion; the effect on volume of RBC and platelet transfusion is uncertain.

Abbreviations: FFP, fresh frozen plasma; PRBC, packed red blood cells; TEG, thromboelastography.* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.P2 Characteristics and results of studies examining the effect of point-of-care testing on transfusion volume.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Ak (2009)	Level II *Fair*	N=224	Adults undergoing elective, first-time CABG with CPB.	Hospital in Turkey	TEG-based algorithm guided transfusion (comprising kaolin-activated (k) TEG and h-kTEG analyses) Comparator was clinician-directed transfusion[1]	Median (IQR) units of PRBCs transfused intraoperatively	1 (0, 1)	0 (0, 1)	P=0.581
						Median (IQR) units of PRBCs transfused postoperatively	1 (0, 1)	1 (0, 1)	P=0.741
						Median (IQR) units of PRBCs transfused both intra-and postoperatively	1 (0, 1)	1 (1, 2)	P=0.599
						Median (IQR) units of FFP transfused intraoperatively	0 (0, 1)	1 (0, 1)	P=0.008
						Median (IQR) units of FFP transfused postoperatively	1 (0, 1)	1 (0, 1)	P=0.034
						Median (IQR) units FFP transfused both intra- and postoperatively	1 (0, 1)	1 (1, 2)	P=0.001
						Median (IQR) units of platelets transfused intraoperatively	0(0, 1)	1 (0, 1)	P=0.004
						Median (IQR) units of platelets transfused postoperatively	1 (0, 1)	1 (0, 1)	P=0.028
						Median (IQR) units of platelets transfused both intra- and postoperatively	1 (1, 1)	1 (1, 2)	P=0.001
Avidan (2004)	Level II (POC vs laboratory test) or Level III (POC vs clinical discretion) *Fair*	POC. N=51 Laboratory test. N=51 Clinical discretion. N=108	Adults undergoing elective, first-time CABG with CPB.	Hospital in UK	Algorithm based on near-patient haemostatic testing. POC devices used include ACT+/Junior, Hepcon HMS Hemostasis Management System, PFA-100 platelet function analyser; and two dual-channel TEG coagulation analysers used in parallel. Randomised comparator was algorithm using routine laboratory haemostatic tests and historical comparator was clinician discretion.	Mean (SD) units of PRBCs transfused for those transfused	POC: 2.9 (NR)	Laboratory: 2.7 (NR) Clinician discretion: 3.1 (NR)	NR
						Median (IQR) volume of PRBCs transfused, mL	POC: 500 (0, 678)	Laboratory: 495 (0, 612) Clinician discretion: 512 (286, 962)	Kruskal-Wallis ANOVA: P=0.03
						Mean (SD) units of platelets transfused for those transfused	POC: 1.5 (NR)	Laboratory: 2.0 (NR) Clinician discretion: 1.0 (NR)	NR

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
						Mean (SD) units of FFP transfused for those transfused	POC: 3.0 (NR)	Laboratory: 0 (0) Clinician discretion: 4.1 (NR)	NR
Royston (2001)	Level II *Poor*	N=60	Adults undergoing cardiac surgery[2]	Hospital in UK	Heparinase-modified TEG-guided intraoperative algorithm. Comparator was transfusion guided by clinical criteria and laboratory-based tests	Volume of blood components transfused	5 units of FFP and 1 pool of platelets	16 units of FFP and 9 platelet pools	P<0.05
Shore-Lesserson (1999)	Level II *Fair*	N=105	Adults undergoing cardiac surgery with a moderate to high risk for requiring a transfusion	Hospital in USA	TEG-guided transfusion algorithm compared with standard laboratory-based transfusion therapy.	Mean (SD) volume of PRBCs transfused (intraoperative), mL	267 (423)	346 (449)	P=0.4
						Mean (SD) volume of PRBCs transfused (postoperative), mL	103 (252)	177 (318)	P=0.27
						Mean (SD) volume of PRBCs transfused (total), mL	354 (487)	475 (593)	P=0.12
						Mean (SD) volume of FFP transfused (intraoperative), mL	22 (101)	113 (407)	P=0.4
						Mean (SD) volume of FFP transfused (postoperative), mL	33 (169)	146 (378)	P=0.13
						Mean (SD) volume of FFP transfused (total), mL	36 (142)	217 (463)	P<0.05
						Mean (SD) volume of platelet concentrates transfused (intraoperative), mL	22 (75)	41 (122)	P=0.6
						Mean (SD) volume of platelet concentrates transfused (postoperative), mL	11 (46)	42 (107)	P=0.3
						Mean (SD) volume of platelet concentrates transfused (total), mL	34 (94)	83 (160)	P=0.16
Westbrook (2009)	Level II *Fair*	N=69	Adults undergoing cardiac surgery with the exception of one patient who underwent lung transplantation	Hospital in Australia	TEG-guided transfusion algorithm vs. clinician directed administration with reference to laboratory coagulation tests	Units of blood products transfused intraoperatively	19	44	ns (p-value not reported)
						Units of blood products transfused in ICU	18	46	ns (p-value not reported)
						Total units of blood products transfused	37	90	ns (p-value not reported)
						Units of PRBCs transfused intraoperatively	11	15	ns (p-value not reported)

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
						Units of PRBCs transfused in ICU	3	18	ns (p-value not reported)
						Total units of PRBCs transfused	14	33	ns (p-value not reported)
						Units of FFP transfused intraoperatively	8	14	ns (p-value not reported)
						Units of FFP transfused postoperatively	10	8	ns (p-value not reported)
						Total units of FFP transfused	18	22	ns (p-value not reported)
						Units of platelets transfused intraoperatively	0	10	ns (p-value not reported)
						Units of platelets transfused postoperatively	5	5	ns (p-value not reported)
						Total units of platelets transfused	5	15	ns (p-value not reported)
						Units of cryoprecipitate transfused intraoperatively	0	5	ns(p-value not reported)
						Units of cryoprecipitate transfused postoperatively	0	15	ns(p-value not reported)
						Total units of cryoprecipitate transfused	0	20	ns(p-value not reported)

Abbreviations: ANOVA, analysis of variance; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; POC, point-of-care; PRBC, packed red blood cells; SD, standard deviation; TEG, thromboelastography.[1] Using criteria obtained from abnormal laboratory tests (PT, APTT and platelet count), absence of visible clots and presence of generalized oozing-type bleeding in the surgical field to determine blood product administration.

[2] Ten per cent of the patients in each series had a heart transplantation and were taking aspirin and/or warfarin immediately before surgery. About 50% of the patients in each group had revascularisation and were also taking aspirin, and required multiple grafts with a bypass time estimated to be greater than 100 minutes. The remaining 40% of the patients were having the Ross procedure, multiple valve or valve and revascularisation surgery. No patients were having repeat operations and none received prophylactic aprotinin, epsilon aminocaproic or tranexamic acid.

[3] Before and after cohort design, single institution.

[4] Bedside instrument measuring clot formation and dissolution indicating changes in coagulation, platelet function, platelet-fibrinogen interaction and fibrinolysis

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on blood loss?		Evidence table ref*: POQ3.I7.P3
1. Evidence base		
Level II evidence: Ak 2009 (fair quality; N=224); Avidan 2004 (fair quality; N=102); Royston 2001 (poor quality; N=60); Shore-Lesserson 1999 (fair quality; N=105); Westbrook 2009 (fair quality; N=69) Level III evidence: Avidan 2004 (fair quality; N=159)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The studies are consistent in finding no significant difference between treatment arms.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
All studies found no significant impact. See Summary Table POQ3.17.P3.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The studies were all conducted in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The studies were conducted in Australia (Westbrook 2009), Turkey (Ak 2009), UK (Avidan 2004; Royston 2001), and USA (Shore-Lesserson 1999).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Avidan 2004 included TEG and other tests in their transfusion algorithm.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Several Level II and III studies with moderate risk of bias.
2. Consistency	B	All studies consistent
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	B	Evidence not directly generalisable to the target population but could be sensibly applied.
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the use of thromboelastography does not appear to have an effect on blood loss.

Abbreviations: NA, not applicable.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.P3 Characteristics and results of studies examining the effect of point-of-care testing on blood loss.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Ak (2009)	Level II *Fair*	N=224	Adults undergoing elective, first-time CABG with CPB.	Hospital in Turkey	TEG-based algorithm guided transfusion (comprising kaolin-activated (k) TEG and h-kTEG analyses) Comparator was clinician-directed transfusion[1]	Mean (SD) 12-hour mediastinal chest tube drainage, mL	480.5 (351)	591.4 (339.2)	P=0.087
Avidan (2004)	Level II (POC vs laboratory test) or Level III (POC vs clinical discretion) *Fair*	POC. N=51 Laboratory. N=51 Clinical discretion. N=108	Adults undergoing elective, first-time CABG with CPB.	Hospital in UK	Algorithm based on near-patient haemostatic testing. POC devices used include ACT+/Junior, Hepcon HMS Hemostasis Management System, PFA-100 platelet function analyser; and two dual-channel TEG coagulation analysers used in parallel. Randomised comparator was algorithm using routine laboratory haemostatic tests and historical comparator was clinician discretion.	Median (IQR) 24-hour postoperative blood loss, mL	POC: 755 (606, 975)	Laboratory: 850 (688, 1095) Clinician discretion: 810 (550, 1295)	NR
Royston (2001)	Level II *Poor*	N=60	Adults undergoing cardiac surgery[1]	Hospital in UK	Heparinase-modified TEG-guided intraoperative algorithm. Comparator was transfusion guided by clinical criteria and laboratory-based tests	Median (IQR) 12-hour chest tube drainage, mL	470 (295, 820)	390 (240, 820)	NR
Shore-Lesserson (1999)	Level II *Fair*	N=105	Adults undergoing cardiac surgery with a moderate to high risk for requiring a transfusion	Hospital in USA	TEG-guided transfusion algorithm compared with standard laboratory-based transfusion therapy.	Mean (SD) six-hour mediastinal drainage, mL	362 (274)	469 (637)	P=0.63
						Mean (SD) 24-hour mediastinal drainage, mL	702 (500)	901 (847)	P=0.27
Westbrook (2009)	Level II *Fair*	N=69	Adults undergoing cardiac surgery with the exception of one patient who underwent lung transplantation	Hospital in Australia	TEG-guided transfusion algorithm vs. clinician directed administration with reference to laboratory coagulation tests	Median (IQR) blood loss, mL	875 (755-1130)	960 (820-1200)	P=0.437

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; IQR, interquartile range; POC, point-of-care testing; NR, not reported; SD, standard deviation; TEG, thromboelastography.

[1] Using criteria obtained from abnormal laboratory tests (PT, APTT and platelet count), absence of visible clots and presence of generalized oozing-type bleeding in the surgical field to determine blood product administration.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on mortality?		Evidence table ref*: POQ3.I7.P4
1. Evidence base		
Level II evidence: Ak 2009 (fair quality; N=224); Shore-Lesserson 1999 (fair quality; N=105) Level III evidence: Spalding 2007 (fair quality; N=1422)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All the studies are consistent in finding no significant impact	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Meta-analysis (conducted herein) of Level II evidence: RR 0.75 (0.19, 3.02); P=0.69; N=329 Meta-analysis (conducted herein) of Level II and III evidence: RR 1.00 (0.67, 1.49); P=1.00; N=1751	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
The studies were all conducted in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The studies were conducted in Turkey (Ak 2009), USA (Shore-Lesserson 1999), and Germany (Spalding 2007).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Included studies were underpowered to detect a mortality difference.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Several Level II and III studies with a moderate risk of bias.
2. Consistency	A	All studies consistent
3. Clinical impact	D	No statistically significant impact
4. Generalisability	B	All studies conducted in adults undergoing cardiac surgery
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on mortality is uncertain.

Abbreviations: NA, not applicable; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.P4 Characteristics and results of studies examining the effect of point-of-care testing on mortality.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Ak (2009)	Level II *Fair*	N=224	Adults undergoing elective, first-time CABG with CPB.	Hospital in Turkey	TEG-based algorithm guided transfusion (comprising kaolin-activated (k) TEG and h-kTEG analyses) Comparator was clinician-directed transfusion[1]	Early mortality (defined as death within 30 days of operation)	3/114 (2.6%) (low cardiac output=2, multiple organ failure=1)	2/110 (1.8%)	P=0.68
Shore-Lesserson (1999)	Level II *Fair*	N=105	Adults undergoing cardiac surgery with a moderate to high risk for requiring a transfusion	Hospital in USA	TEG-guided transfusion algorithm compared with standard laboratory-based transfusion therapy.	Mortality (ITT)	0/53 (0%)	2/52 (4%)	P=0.29
Spalding (2007)	Level III *Fair*	N=1422	Adults undergoing cardiac surgery	Hospital in Germany	TEG vs. no TEG	Early mortality (%)	41/693 (6%)	43/729 (6%)	P=0.99

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ITT, intention-to-treat; TEG, thromboelastography.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on morbidity?			Evidence table ref*: POQ3.I7.P5
1. Evidence base			
Level II evidence: Shore-Lesserson 1999 (fair quality; N=105)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency			
	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact			
Cerebrovascular ischemic event – 1 event in the TEG group (N=53); no events in the control group (N=52); RR 2.94 (0.12, 70.67); P=0.51; N=105	A	Very large	
	B	Substantial	
	C	Moderate	
	D	No difference	
4. Generalisability			
The study was conducted in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability			
The study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One Level II study with moderate risk of bias.
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	No statistically significant impact
4. Generalisability	A	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on morbidity is uncertain.

Abbreviations: CI; confidence interval; RR, relative risk; TEG, thromboelastography.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.P5 Characteristics and results of studies examining the effect of point-of-care testing on morbidity.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Shore-Lesserson (1999)	Level II *Fair*	N=105	Adults undergoing cardiac surgery with a moderate to high risk for requiring a transfusion	Hospital in USA	TEG-guided transfusion algorithm compared with standard laboratory-based transfusion therapy.	Cerebrovascular ischemic event (ITT)	1/53 (2%)	0/52 (0%)	P=0.51

Abbreviations: ITT, intension-to-treat; TEG, thromboelastography.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on quality of life?			Evidence table ref*: POQ3.I7.P6
1. Evidence base			
No evidence found	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency			
	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact			
	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
4. Generalisability			
	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability			
	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the use of thromboelastography on quality of life is unknown.

Abbreviations: NA, not applicable.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on haemoglobin concentration?		Evidence table ref*: POQ3.I7.S1
1. Evidence base		
Level II evidence: Avidan 2004 (fair quality; N=102); Westbrook 2009 (fair quality; N=69) Level III evidence: Avidan 2004 (fair quality; N=159)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
The studies are consistent in finding no significant difference.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Median (IQR); TEG vs comparator Level II evidence: Postoperative Hb concentration (Avidan 2004), g/dL – 9.3 (8.4, 10.3) vs. 9.3 (8.5, 9.7); P=NR; N=102 24 h postoperative Hb concentration (Avidan 2004), g/dL – 10.1 (9, 10.9) vs. 9.9 (9, 10.8); P=NR; N=102 Median (IQR) minimum Hb concentration (Westbrook 2009), g/L– 87 (83, 94) vs. 86 (82, 104); P=NR; N=69 Level III evidence (historical control) 24 h postoperative Hb concentration (Avidan 2004), g/dL – 10.1 (9, 10.9) vs. 10.1 (9.6, 10.8); P=NR; N=159	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
Both studies were conducted in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The studies were conducted in Australia and the UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Avidan 2004 included TEG and other tests in their transfusion algorithm.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Level II and III studies with moderate risk of bias.
2. Consistency	A	All studies consistent
3. Clinical impact	D	No statistically significant impact
4. Generalisability	B	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above

In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on haemoglobin concentration is uncertain.

Abbreviations: NA, not applicable; NR not reported; TEG, thromboelastography.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.S1 Characteristics and results of studies examining the effect of point-of-care testing on haemoglobin concentration.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Avidan (2004)	Level II (POC vs laboratory test) or Level III (POC vs clinical discretion) *Fair*	POC. N=51 Laboratory. N= 51 Clinical discretion. N=108	Adults undergoing elective, first-time CABG with CPB.	Hospital in UK	Algorithm based on near-patient haemostatic testing. POC devices used include ACT+/Junior, Hepcon HMS Hemostasis Management System, PFA-100 platelet function analyser; and two dual-channel TEG coagulation analysers used in parallel. Randomised comparator was algorithm using routine laboratory haemostatic tests and historical comparator was clinician discretion.	Median (IQR) postoperative Hb concentration, g/dL	POC: 9.3 (8.4, 10.3)	Laboratory: 9.3 (8.5, 9.7) Clinician discretion: Not available	NR
						Median (IQR) postoperative 24-hour Hb, g/dL	POC: 10.1 (9, 10.9)	Laboratory: 9.9 (9, 10.8) Clinician discretion: 10.1 (9.6, 10.8)	NR
Westbrook (2009)	Level II *Fair*	N=69	Adults undergoing cardiac surgery with the exception of one patient who underwent lung transplantation	Hospital in Australia	TEG-guided transfusion algorithm vs. clinician directed administration with reference to laboratory coagulation tests	Median (IQR) minimum Hb concentration, g/l	87 (83-94)	86 (82-104)	NS (p value not reported)

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; Hb, haemoglobin; IQR, interquartile range; NR, not reported; NS, not significant; POC, point-of-care testing; TEG, thromboelastography.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on reoperation for bleeding?		Evidence table ref*: POQ3.I7.S2
1. Evidence base		
Level II evidence: Ak 2009 (fair quality; N=224); Avidan 2004 (fair quality; N=102); Shore-Lesserson 1999 (fair quality; N=105) Level III evidence: Avidan 2004 (fair quality; N=159)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
All the studies are consistent in finding no significant impact.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Meta-analysis (conducted herein) of Level II evidence: RR 0.86 (0.33, 2.25); P=0.76; N=431	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The studies were conducted in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The studies were conducted in Turkey (Ak 2009), the UK (Avidan 2004), and the USA (Shore-Lesserson 1999).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

Avidan 2004 included TEG and other tests in their transfusion algorithm.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Several Level II and III studies with moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	No statistically significant impact
4. Generalisability	B	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on the risk of reoperation for bleeding is uncertain.

Abbreviations: CI, confidence interval; NA, not applicable; RR, relative risk.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.S2 Characteristics and results of studies examining the effect of point-of-care testing on reoperation for bleeding.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Ak (2009)	Level II *Fair*	N=224	Adults undergoing elective, first-time CABG with CPB.	Hospital in Turkey	TEG-based algorithm guided transfusion (comprising kaolin-activated (k) TEG and h-kTEG analyses) Comparator was clinician-directed transfusion[1]	Re-exploration for bleeding	6/114 (5%) (causes all surgical)	5/110 (5%) (Causes, 2= surgical, 3 inappropriate surgical intervention for bleeding)	NR
Avidan (2004)	Level II (POC vs laboratory test) or Level III (POC vs clinical discretion) *Fair*	POC. N=51 Laboratory. N=51 Clinical discretion. N=108	Adults undergoing elective, first-time CABG with CPB.	Hospital in UK	Algorithm based on near-patient haemostatic testing. POC devices used include ACT+/Junior, Hepcon HMS Hemostasis Management System, PFA-100 platelet function analyser; and two dual-channel TEG coagulation analysers used in parallel. Randomised comparator was algorithm using routine laboratory haemostatic tests and historical comparator was clinician discretion.	Reoperation for bleeding	POC: 1/51 (2%)	Laboratory: 1/51 (2%) Clinician discretion: 3/108 (3%)	POC vs. laboratory RR (95% CI): 1.00 (0.06, 15.56); P=1.00 POC vs. clinician discretion RR (95% CI): 0.71 (0.08, 6.62); P=0.76
Shore-Lesserson (1999)	Level II *Fair*	N=105	Adults undergoing cardiac surgery with a moderate to high risk for requiring a transfusion	Hospital in USA	TEG-guided transfusion algorithm compared with standard laboratory-based transfusion therapy.	Reoperation for bleeding	0/53 (0%)	2/52 (4%)[2]	P=0.29

Abbreviations: CI, confidence interval; POC, point-of-care testing; RR, relative risk; TEG, thromboelastography.

[1] Using criteria obtained from abnormal laboratory tests (PT, APTT and platelet count), absence of visible clots and presence of generalised oozing-type bleeding in the surgical field to determine blood product administration.

[2] In one patient, a specific surgical source of bleeding was discovered.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on coagulation status?		Evidence table ref*: POQ3.I7.S3
1. Evidence base		
Level II evidence: Shore-Lesserson 1999 (fair quality; N=105)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Not applicable	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
No significant impact found See Summary Table POQ3.17.S3	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
The study conducted in adults undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One fair quality Level II study with moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	No statistically significant impact
4. Generalisability	A	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on coagulation status is uncertain.

Abbreviations: NA, not applicable.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.S3 Characteristics and results of studies examining the effect of point-of-care testing on coagulation status.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Shore-Lesserson (1999)	Level II *Fair*	N=105	Adults undergoing cardiac surgery with a moderate to high risk for requiring a transfusion	Hospital in USA	TEG-guided transfusion algorithm compared with standard laboratory-based transfusion therapy.	Mean (SD) activated clotting time (baseline), seconds	165 (34)	170 (49)	P=0.55
						Mean (SD) activated clotting time (post-protamine), seconds	158 (93)	149 (20)	P=0.50
						Mean (SD) platelet count (baseline), X1000/μL	203 (66)	200 (78)	P=0.83
						Mean (SD) platelet count (warming on CPB), X1000/μL	92 (79)	96 (79)	P=0.80
						Mean (SD) platelet count (ICU), X1000/μL	111 (48)	120 (48)	P=0.34
						Mean (SD) prothrombin time (baseline), seconds	13.0 (1.1)	12.9 (1.3)	P=0.67
						Mean (SD) prothrombin time (post-protamine), seconds	18.1 (2.3)	21.3 (26)	P=0.38
						Mean (SD) prothrombin time (ICU), seconds	16.1 (1.7)	15.7 (1.6)	P=0.22
						Mean (SD) activated partial thromboplastin time (baseline), seconds	31.6 (6.9)	34.1 (13.1)	P=0.23
						Mean (SD) activated partial thromboplastin time (post-protamine), seconds	52.2 (48.0)	43.0 (14)	P=0.19
						Mean (SD) activated partial thromboplastin time (ICU), seconds	35.9 (6.1)	36.8 (10.2)	P=0.59
						Mean (SD) fibrinogen concentration (baseline), mg/dL	409 (82)	416 (118)	P=0.73
						Mean (SD) fibrinogen concentration (post-protamine), mg/dL	239 (86)	246 (86)	P=0.68
						Mean (SD) fibrinogen concentration (ICU), mg/dL	259 (95)	263 (118)	P=0.85

Abbreviations: ICU, intensive care unit; SD, standard deviation; TEG, thromboelastography.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on length of hospital stay?		Evidence table ref*: POQ3.I7.S5
1. Evidence base		
Level II evidence: Westbrook 2009 (fair quality; N=69)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Median (IQR) length of hospital stay (TEG vs clinician discretion), days: 9 (7, 3) vs. 8 (7, 12); P=NS (P-value not reported)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The study was conducted in patients undergoing cardiac surgery with the exception of one patient who underwent lung transplantation.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The study was conducted in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One Level II study with moderate risk of bias.
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	A	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	A	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on length of hospital stay is uncertain.

Abbreviations: IQR, interquartile range; NA, not applicable; NS, not significant; TEG, thromboelastography.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.S5 Characteristics and results of studies examining the effect of point-of-care testing on hospital length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Westbrook (2009)	Level II *Fair*	N=69	Adults undergoing cardiac surgery with the exception of one patient who underwent lung transplantation	Hospital in Australia	TEG-guided transfusion algorithm vs. clinician directed administration with reference to laboratory coagulation tests	Median (IQR) length of hospital stay, days	9 (7, 3) *Extra day not due to bleeding	8 (7, 12)	NS (P-value NR)

Abbreviations: IQR, interquartile range; NR, not reported; NS, not significant; TEG, thromboelastography.

Key question(s): In patients undergoing surgery, what is the effect of point-of-care testing on ICU admission and length of stay?		Evidence table ref*: POQ3.I7.S6
1. Evidence base		
Level II evidence: Westbrook 2009 (fair quality; N=69)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Median (IQR) length of ICU stay (TEG vs clinician discretion), hours: 29.4 (14.3, 56.4) vs. 32.5 (22, 74.5); P=NS (P-value not reported)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
The study was conducted in patients undergoing cardiac surgery with the exception of one patient who underwent lung transplantation.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
The study was conducted in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One Level II study with moderate risk of bias.
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	No statistically significant impact.
4. Generalisability	A	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	A	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on length of ICU stay is uncertain.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable; NS, not significant; TEG, thromboelastography.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I7.S6 Characteristics and results of studies examining the effect of point-of-care testing on length of ICU stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		
							Intervention	Comparator	p-value
Westbrook (2009)	Level II *Fair*	N=69	Adults undergoing cardiac surgery with the exception of one patient who underwent lung transplantation	Hospital in Australia	TEG-guided transfusion algorithm vs. clinician directed administration with reference to laboratory coagulation tests	Median (IQR) length of ICU stay, hours	29.4 (14.3, 56.4)	32.5 (22, 74.5)	NS (P-value NR)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NR, not reported; NS, not significant; TEG, thromboelastography.

Recommendation(s) for point-of-care testing using thromboelastography

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In adult patients undergoing cardiac surgery, the use of thromboelastography should be considered.	C	PO3.I7.P1, PO3.I7.P2

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Increased use of TEG and related devices.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Capital investment, training and staffing (technicians).		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Significant cost.		
What could help to facilitate implementation of the recommendation?	YES	NO
Targeted funding for equipment.		

Intervention 8 – Administration of antifibrinolytics & DDAVP: Aprotinin

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on transfusion incidence?		Evidence table ref[a]: POQ3.I8a.P1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality), four supportive level I studies (Henry 2009/good quality; Brown 2007; fair quality; Kagoma 2009/good quality; McIlroy 2009 /good quality) and one supportive Level I/II study[c] (Gurusamy 2009/good-fair quality). In addition, three additional RCTs (Later 2009/good quality; Nurözler 2008/fair quality; Colwell 2007/good quality) were identified that were published following the Henry 2007 literature search that were not included in any of the supportive Level I studies.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Additional RCT results consistent. Pivotal evidence – Henry 2007 Moderate to substantial heterogeneity between studies. Appears to be due to differences in magnitude of effect rather than lack of effect in some studies. May also be due to different surgery types assessed.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – RR 0.66 (0.62, 0.71); 43.8% vs 64.3%; 96 RCTs (N=9949) Cardiac surgery – RR 0.66 (0.61, 0.72); 45.6% vs 66.1%; 76 RCTs (N=8793) Orthopaedic surgery – RR 0.69 (0.56, 0.85); 23.1% vs 43.9%; 13 RCTs (N=771) Liver surgery – RR 0.58 (0.37, 0.90); 24.1% vs 43.3%; 2 RCTs (N=177) Supportive evidence –see Summary Table POQ3.I8a.P1	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis; 76/96 studies in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

The Henry (pivotal) review assessed quality and performed a subgroup analysis of transfusion incidence for all surgery types based on the rating (A,B or C) of treatment allocation[b]. The analysis showed no substantial difference in the results between studies rated A, B or C.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I (good quality), four supportive level I studies, one supportive Level I/II study[c] and three additional RCTs.
2. Consistency	B	Significant heterogeneity in the pivotal level I study but mostly due to difference in magnitude of effect and not direction of effect. Differences may be due to different surgery types. Results of supportive level I studies and additional RCTs consistent with pivotal evidence.
3. Clinical impact	B	There were significant differences between intravenous aprotinin therapy and no therapy overall and for surgery subgroups. Substantial clinical impact.
4. Generalisability	B	The results are generalisable to an adult surgical population; the majority of studies were conducted in patients undergoing cardiac surgery.
5. Applicability	B	Overall there were a large number of studies conducted in a wide range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy reduces the incidence of allogeneic blood transfusion compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[b] Cochrane ratings defined as follows: Grade A, adequate allocation concealment; Grade B, uncertain allocation concealment; Grade C, inadequate allocation concealment.
[c] A supportive level I/II study represents a systematic review which identified only one relevant RCT.

POQ3.I8a.P1 Characteristics and results of studies examining the effect of aprotinin on transfusion incidence.

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	96 RCTs N=9949	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 0.66 (0.62, 0.71)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=68%)
Henry (2007)	Level I *Good*	16 RCTs N=1251	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Prime dose aprotinin (IV) vs no aprotinin[d]	Transfusion incidence (allogeneic blood)	RR 0.83 (0.71, 0.96)	*Favours aprotinin* 0.014	*Substantial* P*het*<0.001 (I^2=75%)
		43 RCTs N=3073	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Low dose aprotinin (IV) vs no aprotinin[e]	Transfusion incidence (allogeneic blood)	RR 0.66 (0.59, 0.74)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=53%)
		56 RCTs N=6569	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	High dose aprotinin (IV) vs no aprotinin[f]	Transfusion incidence (allogeneic blood)	RR 0.65 (0.60, 0.71)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=66%)
Henry (2007)	Level I *Good*	76 RCTs N=8768	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin with transfusion protocol	Transfusion incidence (allogeneic blood)	RR 0.65 (0.60, 0.70)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=70%)
		20 RCTs N=1182	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin without transfusion protocol	Transfusion incidence (allogeneic blood)	RR 0.73 (0.62, 0.86)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=59%)
Henry (2007)	Level I *Good* Rating A[g]	27 RCTs N=2113	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	OR 0.65 (0.54, 0.78)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=84%)
	Level I *Good* Rating B[g]	57 RCTs N=6993	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	OR 0.68 (0.63 0.73)	*Favours aprotinin* <0.001	*Moderate* P*het*=0.75 (I^2=48%)
	Level I *Good* Rating C[g]	12 RCTs N=799	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	OR 0.60 (0.49, 0.73)	*Favours aprotinin* <0.001	*Moderate* P*het*=0.13 (I^2=32%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
Cardiac surgery									
Henry (2007)	Level I *Good*	76 RCTs N=8793	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 0.66 (0.61, 0.72)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=71%)
Henry (2007)	Level I *Good*	15 RCTs N=1191	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Prime dose aprotinin (IV) vs no aprotinin[d]	Transfusion incidence (allogeneic blood)	RR 0.81 (0.69, 0.96)	*Favours aprotinin* 0.012	*Substantial* P*het*<0.001 (I^2=78%)
		24 RCTs N=1995	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Low dose aprotinin (IV) vs no aprotinin[e]	Transfusion incidence (allogeneic blood)	RR 0.67 (0.58, 0.77)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=62%)
		55 RCTs N=6533	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	High dose aprotinin (IV) vs no aprotinin[f]	Transfusion incidence (allogeneic blood)	RR 0.66 (0.60, 0.72)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=67%)
Henry (2009)	Level I *Good*	81 RCTs N=9139[h]	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[b]	Aprotinin (IV) vs placebo	Transfusion incidence (allogeneic blood)	RR 0.66 (0.61, 0.72)	*Favours aprotinin* <0.05	*NR*
Brown (2007)	Level I *Fair*	49 RCTs N=4379	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	High dose aprotinin (IV) vs placebo[i]	Transfusion incidence (pRBCs)	RR 0.60 (0.53, 0.67)	*Favours aprotinin* <0.001	*NR*
		20 RCTs N=1645	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Low dose aprotinin (IV) vs placebo[i]	Transfusion incidence (pRBCs)	RR 0.76 (0.66, 0.86)	*Favours aprotinin* <0.001	*NR*
McIlroy (2009)	Level I *Good*	10 RCTs N=856	Adult patients undergoing cardiac surgery receiving ASA	Hospital – planned surgery Various countries	Aprotinin (IV) vs placebo	Transfusion incidence (allogeneic blood)	OR 0.34 (0.25, 0.46)	*Favours aprotinin* <0.001	*None* P*het*=0.75 (I^2=0%)
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- and intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High-dose aprotinin (IV) vs placebo[i]	Transfusion incidence (pRBCs)	50% vs 70.9%	*Favours aprotinin* 0.004	*NA*
						Transfusion incidence (blood products)	61.5% vs 78.6%	*Favours aprotinin* 0.009	*NA*
Nurözler (2008)	Level II *Fair*	1 RCT N=51	Adult patients undergoing off-pump coronary bypass who have received clopidogrel within 5 days of surgery	Hospital – planned surgery Turkey	Low-dose aprotinin (IV) vs placebo[k]	Transfusion incidence (RBC)	68% vs 88%	*Favours aprotinin* 0.014	*NA*
						Transfusion incidence (blood products)	28% vs 53%	*Favours aprotinin* 0.002	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
Orthopaedic surgery									
Henry (2007)	Level I *Good*	13 RCTs N=771	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 0.69 (0.56, 0.85)	*Favours aprotinin* <0.001	*None* P*het*=0.23 (I^2=21%)
Kagoma (2009)	Level I *Good*	3 RCTs N=347	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Transfusion incidence	RR 0.63 (0.50, 0.80)	*Favours aprotinin* <0.05	*NR*
Colwell (2007)	Level II *Good*	1 RCT N=352	Adults undergoing unilateral total hip arthroplasty	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion incidence (whole blood or RBCs)	17% vs 32%	*Favours aprotinin* 0.0009	*NA*
		1 RCT N=352	Adults undergoing unilateral total hip arthroplasty	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion incidence (allogeneic blood)	11% vs 22%	*Favours aprotinin* 0.006	*NA*
		1 RCT N=278	Adults undergoing unilateral total hip arthroplasty	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion incidence (whole blood or RBCs without donation)	13% vs 24%	*Favours aprotinin* 0.02	*NA*
		1 RCT N=74	Adults undergoing unilateral total hip arthroplasty	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion incidence (whole blood or RBCs with donation)	32% vs 62%	*Favours aprotinin* ND	*NA*
Liver surgery									
Henry (2007)	Level I *Good*	2 RCTs N=177	Adult patients undergoing liver surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 0.58 (0.37, 0.90)	*Favours aprotinin* 0.015	*None* P*het*=0.31 (I^2=3%)
Gurusamy (2009)	Level I/II *Good/Fair*	1 RCT N=37	Adult patients undergoing liver resection	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Transfusion incidence (allogeneic blood)	RR 0.43 (0.21, 0.89)	*Favours aprotinin* 0.02	*NA* P*het*=NA (I^2=NA)
Other surgery									
Henry (2007)	Level I *Good*	2 RCTs N=62	Adult patients undergoing thoracic surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 0.28 (0.11, 0.74)	*Favours aprotinin* 0.011	*None* P*het*=0.54 (I^2=0%)
Henry (2007)	Level I/II *Good/Good*	1 RCT N=60	Adult patients undergoing vascular surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 1.01 (0.72, 1.40)	*No difference* 0.98	*None* P*het*=NA (I^2=NA)

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
Henry (2007)	Level I/II *Good/Poor*	1 RCT N=56	Adult patients undergoing neurosurgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 0.73 (0.40, 1.35)	*No difference* 0.32	*NA* P*het*=NA (I^2=NA)
Henry (2007)	Level I/II *Good/Poor*	1 RCT N=30	Adult patients undergoing orthognathic surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Transfusion incidence (allogeneic blood)	RR 0.11 (0.02, 0.77)	*Favours aprotinin* 0.026	*NA* P*het*=NA (I^2=NA)
PAEDIATRIC POPULATION/IV APROTININ									
Orthopaedic surgery									
Tzortzopoulou (2008)	Level II *Good*	1 RCT N=43	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Transfusion incidence	RR 0.75 (0.44, 1.27)	*No difference* 0.28	*NA*
ADULT POPULATION/TOPICAL APROTININ									
Cardiac surgery									
Abrishami (2009)	Level I *Good*	3 RCTs N=341	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Aprotinin (topical) vs placebo	Transfusion incidence (allogeneic RBC)	RR 0.72 (0.47, 1.08)	*No difference* 0.11	*Substantial* Phet=0.008 (I^2=60%)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.

Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; ND, not determined; NR, not reported; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.

[d] Prime' dose included regimens that added aprotinin to the pump prime solution of the cardiopulmonary bypass exclusively. 12/16 trials studied a 'prime' dose pf 2 million KIU, 2/16 trials studied a 'prime' dose of 1 million KIU, 1/16 trials studied a 'prime' dose of 500,000 KIU and 1/16 trials studies a 'prime' dose of 25,000 KIU/kg.

[e] Low-dose aprotinin was defined as any regimen that did not follow the 'full Hammersmith' regimen, including those studies that described their regimen as 'half Hammersmith'. For non-cardiac surgery trials, regimens were classified as low dose if the total dose was < 5 million KIU or 700 mg aprotinin.

[f] High-dose aprotinin was defined as any regimen that was described as the 'full Hammersmith' regimen. For non-cardiac surgery trials, regimens were classified as high-dose if the total dose was ≥ 5 million KIU or 700 mg aprotinin.

[g] Cochrane ratings defined as follows: Grade A, adequate allocation concealment; Grade B, uncertain allocation concealment; Grade C, inadequate allocation concealment.

[h] Total number of trials available for analysis. The actual number of trials included in the analysis is not reported.

[i] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.

[j] Low dose (half-dose) aprotinin consisted of a 1 million KIU IV loading dose, 1 million KIU pump-priming dose, and 0.25 million KIU IV/h maintenance dose.

[k] Low dose aprotinin consisted of 1 million KIU infused over 30 min followed by a continuous infusion of 0/5 million KIU/h until the end of surgery.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on transfusion volume?		Evidence table ref[a]: POQ3.I8a.P2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) study which included data from 35 RCTs which provides data on the transfusion volume in patients who received transfusion. There was one pivotal Level I study (Henry 2007/good quality/61 RCTs) and five additional RCTs published following the Henry review (Later 2009/good quality; Nurözler 2008/fair quality; Colwell 2007/good quality; Apostolakis 2008/fair quality; Leijdekkers 2006/fair quality) which provide data on transfusion volume in all patients (transfused or not transfused).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Consistency of individual studies within meta-analyses described below. Additional RCTs consistent. Pivotal evidence – Henry 2007 Moderate to substantial heterogeneity between studies. Heterogeneity could be due to differences in surgery types, degree of bleeding expected with different surgery types and transfusion triggers used in each study. Supportive evidence –see Summary Table POQ3.I8a.P1	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (transfused patients only) – WMD -0.96 units (-1.24, -0.68); 35 RCTs (N=3363) Supportive evidence –see Summary Table POQ3.I8a.P1	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

The most relevant data comes from the Henry 2007 pivotal review which assessed transfusion volume in transfused patients only (ie, takes out effect of patients who received no transfusion). Heterogeneity was discussed by the CRG and it was concluded that it may be related to degree of bleeding, surgery type and transfusion triggers.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I (good quality) study which provides data on the transfusion volume in patients who received transfusion (includes 35 RCTs). There was one pivotal Level I (good quality) study and five additional RCTs which provide data on transfusion volume in all patients (transfused or not transfused).
2. Consistency	B	Most studies were reasonably consistent. Some differences which may be related to differences in surgery type, degree of bleeding and transfusion triggers.
3. Clinical impact	B	There was a significant difference in transfusion volume between intravenous aprotinin therapy and no therapy when only transfused patients were considered. There were significant differences between intravenous aprotinin therapy and no therapy overall and for surgery subgroups in transfused + non-transfused patients.
4. Generalisability	B	The results are generalisable to an adult surgical population.
5. Applicability	B	Overall there were a large number of studies conducted in a wide range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy reduces the volume of allogeneic blood transfusion compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.P2 Characteristics and results of studies examining the effect of aprotinin on transfusion volume

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (mean ± SD) vs control (mean ± SD)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	61 RCTs N=6780	Adult patients undergoing any surgery (all patients)	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Transfusion volume (units; allogeneic blood)	WMD -1.07 (-1.31, -0.83)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=90%)
		35 RCTs N=3363	Adult patients undergoing any surgery (transfused patients only)	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Transfusion volume (units; allogeneic blood)	WMD -0.96 (-1.24, -0.68)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=60%)
Cardiac surgery									
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- or intermediate-risk cardiac surgery (all patients)	Hospital – planned surgery The Netherlands	High-dose aprotinin (IV) vs placebo[d]	Transfusion volume (units; pRBCs)	MD -1.0 (-1.0, 0)	Favours aprotinin <0.001	*NA*
Nurözler (2008)	Level II *Fair*	1 RCT N=51	Adult patients undergoing off-pump coronary bypass who have received clopidogrel within 5 days of surgery (all patients)	Hospital – planned surgery Turkey	Low-dose aprotinin (IV) vs placebo[e]	Transfusion volume (units; pRBC)	1.7 ± 1.4 vs 2.9 ± 1.8	*Favours aprotinin* 0.014	*NA*
						Transfusion incidence (units; platelets)	0.4 ± 0.6 vs 2.3 ± 1.2	*Favours aprotinin* 0.002	*NA*
						Transfusion incidence (units; FFP)	0.6 ± 0.3 vs 1.4 ± 0.6	*Favours aprotinin* 0.008	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (mean ± SD) vs control (mean ± SD)	*Significance* P-value	
Orthopaedic surgery									
Colwell (2007)	Level II *Good*	1 RCT N=352	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion volume (whole blood or RBCs)	0.27 vs 0.63	*Favours aprotinin* 0.0003	*NA*
		1 RCT N=352	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion volume (allogeneic blood)	0.17 vs 0.42	*Favours aprotinin* 0.004	*NA*
		1 RCT N=278	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion volume (whole blood or RBCs without donation)	0.21 vs 0.46	*Favours aprotinin* 0.0153	*NA*
		1 RCT N=74	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Transfusion volume (whole blood or RBCs with donation)	0.52 vs 1.21	*Favours aprotinin* ND	*NA*
Other surgery									
Apostolakis (2008)	Level II *Fair*	1 RCT N=59	Adult patients undergoing thoracic surgery (all patients)	Hospital – planned surgery Greece	Ultra-low-dose aprotinin (IV) vs placebo[f]	Intraoperative transfusion volume (units; pRBCs)	0.17 ± 0.54 vs 0.17 ± 0.53	No difference 0.967	*NA*
						Postoperative transfusion volume (units; pRBCs)	0.00 ± 0.00 vs 0.03 ± 0.18	No difference 0.970	*NA*
						Intraoperative transfusion volume (units; FFP)	0.21 ± 0.62 vs 0.20 ± 0.76	No difference 0.330	*NA*
						Postoperative transfusion volume (units; FFP)	0.21 ± 0.62 vs 0.87 ± 1.53	*Favours aprotinin* 0.035	*NA*
Leijdekkers (2006)	Level II *Fair*	1 RCT N=35	Adult patients undergoing surgery for infra-renal abdominal aneurysm (all patients)	Hospital – planned surgery The Netherlands	Aprotinin (IV) vs placebo	Mean total infusion (mL)	7845 ± 4888 vs 7835 ± 4776	*No difference* 0.99	*NA*
						Mean packed cells (units)	4.1 ± 3.1 vs 4.1 ± 2.9	*No difference* 0.95	*NA*
						Mean FFP (units)	0.5 ±0.9 vs 0.3 ± 0.8	*No difference* 0.35	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (mean ± SD) vs control (mean ± SD)	*Significance* P-value	
PAEDIATRIC POPULATION/IV APROTININ									
Schouten (2009)	Level I *Fair*	3 RCTs N=250	Paediatric patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Transfusion volume (mL/kg; pRBCs)	WMD -4 (-7, -2)	*Favours aprotinin* NR	*None* P*het*=NR (I^2=0%)
	Level I *Fair*	2 RCTs N=228	Paediatric patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Transfusion volume (mL/kg; plasma)	WMD -5 (-8, -2)	*Favours aprotinin* NR	*None* P*het*=NR (I^2=0%)
Tzortzopoulou (2008)	Level I *Good*	2 RCTs N=87	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Transfusion volume (mL)	WMD -361 (-584, -139)	*Favours aprotinin* 0.0015	*None* P*het*=0.80 (I^2=0%)
ADULT POPULATION/TOPICAL APROTININ									
Cardiac surgery									
Abrishami (2009)	Level I *Good*	4 RCTs N=229	Adult patients undergoing primary on-pump cardiac surgery	Hospital – planned surgery Unknown	Aprotinin (topical) vs placebo	Transfusion volume (allogeneic RBC)	WMD -0.83 (-1.21, -0.44)	*Favours aprotinin* <0.001	*None* Phet=0.34 (I^2=11%)
Mehraien (2009)	Level II *Good*	1 RCT N=128	Adult patients undergoing first-time CABG (all patients)	Hospital – planned surgery Iran	Aprotinin (topical) vs placebo	Mean packed cells (units)	0.5 ± 0.7 vs 1.7 ± 1.0	Favours aprotinin 0.002	

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; *het*, heterogeneity; IV, intravenous; kg, kilogram; mL, millilitre; ND, not determined (small sample size); NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; SMD, standardised mean difference; WMD, weighted mean difference.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.

[d] High dose aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.

[e] Low dose aprotinin consisted of 1 million KIU infused over 30 min followed by a continuous infusion of 0/5 million KIU/h until the end of surgery.

[f] Ultra-low dose aprotinin defined as a test dose of 1mL at intubation, followed by 0.5 million IU over 15 min following intubation, and again following closure.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on blood loss?			Evidence table ref[a]: POQ3.I8a.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
There is one pivotal Level I study (Henry 2007/good quality) which included up to 79 RCTs depending on the specific blood loss outcome assessed, three supportive Level I studies (Brown 2007/fair quality; Kagoma 2009/good quality; McIlroy 2009/good quality), one supportive Level I/II study (Gurusamy 2009/good-fair quality) and six additional RCTs (Grant 2008/fair quality; Later 2009/good quality; Nurözler 2008/fair quality; Colwell 2007/good quality; Apostolakis 2008/fair quality; Leijdekkers 2006/fair quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Additional RCT results consistent. Pivotal evidence – Henry 2007 Moderate to substantial heterogeneity between studies. May be due to different surgery types assessed. Supportive evidence –see Summary Table POQ3.I8a.P3	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Pivotal evidence – Henry 2007 Any surgery (total blood loss) – WMD -414 mL (-520, -309); 15 RCTs (N=1577) Cardiac surgery (total blood loss) – WMD -489 mL (-571, -407); 5 RCTs (N=1147) Orthopaedic surgery (total blood loss) – WMD -399 mL (-563, -235); 10 RCTs (N=430) Liver surgery (total blood loss) – WMD -1200 mL (-2943, -543); 2 RCTs (N=137) Other surgery/outcomes and supportive evidence –see Summary Table POQ3.I8a.P3	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Hospital setting. The pivotal review states that overall, studies were conducted in a wide range of countries. It was not possible to determine the location of each of the individual studies from the review.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

A 400 mL difference in blood loss was considered to represent a moderate clinical impact by the CRG.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), three supportive Level I studies, one supportive Level I/II study and six additional RCTs.
2. Consistency	B	Significant heterogeneity in the pivotal level I study but mostly due to difference in magnitude of effect and not direction of effect. Differences may be due to different surgery types. Results of supportive level I studies and additional RCTs consistent with pivotal evidence.
3. Clinical impact	C	There were significant (or near significant) differences in blood loss for all surgery types. The clinical impact was considered to be moderate.
4. Generalisability	B	The results are generalisable to an adult surgical population.
5. Applicability	B	Overall there were a large number of studies conducted in a wide range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy reduces blood loss compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[b] A Level I/II study is a systematic review which included only one RCT.

POQ3.I8a.P3 Characteristics and results of studies examining the effect of aprotinin on blood loss

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (mean ± SD) vs control (mean ± SD)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	15 RCTs N=1577	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Total blood loss (mL)	WMD -414 (-520, -309)	*Favours aprotinin* <0.001	*Substantial* *Phet*=0.003 (I^2=57%)
		13 RCTs N=722	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Intraoperative blood loss (mL)	WMD -185 (-280, -90)	*Favours aprotinin* <0.001	*Substantial* *Phet*<0.001 (I^2=67%)
		79 RCTs N=7414	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Postoperative blood loss (mL)	WMD -358 (-404, -313)	*Favours aprotinin* <0.001	*Substantial* *Phet*<0.001 (I^2=86%)
Cardiac surgery									
Henry (2007)	Level I *Good*	5 RCTs N=1147	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Total blood loss (mL)	WMD -489 (-571, -407)	*Favours aprotinin* <0.001	*None* *Phet*=0.62 (I^2=0%)
		5 RCTs N=360	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Intraoperative blood loss (mL)	WMD -140 (-244, -36)	*Favours aprotinin* 0.0086	*Substantial* *Phet*=0.01 (I^2=68%)
		68 RCTs N=6948	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Postoperative blood loss (mL)	WMD -385 (-432, -339)	*Favours aprotinin* <0.001	*Substantial* *Phet*<0.001 (I^2=85%)
Henry (2007)	Level I *Good*	15 RCTs N=1158	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Prime dose aprotinin (IV) vs no aprotinin[d]	Postoperative blood loss (mL)	WMD -343 (-458, -228)	*Favours aprotinin* <0.001	*Substantial* *Phet*<0.001 (I^2=88%)
		21 RCTs N=1781	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Low dose aprotinin (IV) vs no aprotinin[e]	Postoperative blood loss (mL)	WMD -293 (-349, -238)	*Favours aprotinin* <0.001	*Substantial* *Phet*<0.001 (I^2=61%)
		48 RCTs N=4819	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	High dose aprotinin (IV) vs no aprotinin[f]	Postoperative blood loss (mL)	WMD -428 (-485, -371)	*Favours aprotinin* <0.001	*Substantial* *Phet*<0.001 (I^2=85%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (mean ± SD) vs control (mean ± SD)	*Significance* P-value	
Brown (2007)	Level I *Fair*	22 RCTs N=1760	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	High dose aprotinin (IV) vs placebo[g]	Total blood loss (mL)	WMD -348 (-416, -281)	*Favours aprotinin* <0.001	*NR*
		6 RCTs N=515	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Low dose aprotinin (IV) vs placebo[h]	Total blood loss (mL)	WMD -226 (-277, -175)	*Favours aprotinin* <0.001	*NR*
McIlroy(2009)	Level I *Good*	12 RCTs N=992	Adult patients receiving ASA undergoing cardiac surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Postoperative chest tube blood loss (mL)	WMD -433 (-544, -321)	*Favours aprotinin* <0.001	*Substantial* P*het*<0.001 (I^2=74%)
Grant (2008)	Level II *Fair*	1 RCT N=120	Adult patients undergoing off-pump coronary artery bypass surgery	Hospital – planned surgery US	Aprotinin (IV) vs placebo	Intraoperative blood loss (mL)	867 ± 413[i] and 870 ± 383[j] vs 1252 ± 380	*Favours aprotinin* <0.02	*NA*
						Postoperative blood loss (mL/24 hrs)	415 ± 330[i] and 427 ± 171[j] vs 716 ± 336	*Favours aprotinin* <0.003	*NA*
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- or intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High-dose aprotinin (IV) vs placebo[g]	Mediastinal chest tube drain loss (mL)	MD -295 (-410, -185)	*Favours aprotinin* <0.001	*NA*
Nurözler (2008)	Level II *Fair*	1 RCT N=51	Adult patients undergoing off-pump coronary bypass who have received clopidogrel within 5 days of surgery (all patients)	Hospital – planned surgery Turkey	Low-dose aprotinin (IV) vs placebo[k]	Drainage (mL/24 hr)	423 ± 178 vs 748 ± 212	*Favours aprotinin* 0.005	*NA*
Orthopaedic surgery									
Henry (2007)	Level I *Good*	10 RCTs N=430	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Total blood loss (mL)	WMD -399 (-563, -235)	*Favours aprotinin* <0.001	*Substantial* P*het*=0.01 (I^2=60%)
		5 RCTs N=201	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Intraoperative blood loss (mL)	WMD -151 (-318, 16)	*No difference* 0.076	*Moderate* P*het*=0.16 (I^2=40%)
		7 RCTs N=318	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Postoperative blood loss (mL)	WMD -114 (-224, -3.5)	*Favours aprotinin* 0.043	*Substantial* P*het*=0.005 (I^2=68%)
Kagoma (2009)	Level I *Good*	4 RCTs N=230	Adults undergoing total knee or hip replacement	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Total bleeding[l] (mL)	WMD -639 (-725, -536)	*Favours aprotinin* NR	*NR*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (mean ± SD) vs control (mean ± SD)	*Significance* P-value	
Colwell (2007)	Level II *Good*	1 RCT N=352	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Intraoperative blood loss (mL)	331 vs 385	*Favours aprotinin* 0.0217	*NA*
						0-6 hr drainage (mL)	96 vs 177	*Favours aprotinin* 0.0003	*NA*
						Total drainage (mL)	276 vs 390	*Favours aprotinin* 0.0141	*NA*
						Total fluid loss (mL)	709 vs 957	*Favours aprotinin* 0.0002	*NA*
Liver surgery									
Henry (2007)	Level I *Good*	2 RCTs N=137	Adult patients undergoing liver surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Intraoperative blood loss (mL)	WMD -1200 (-2943, -543)	*Favours aprotinin* 0.02	*Substantial* P*het*=0.02 (I^2=67%)
	Level I/II *Fair*	1 RCT N=24	Adult patients undergoing liver surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Postoperative blood loss (mL)	WMD -105 (-194, -16)	*Favours aprotinin* 0.021	*NA*
Gurusamy (2009)	Level I/II *Good/Fair*	1 RCT N=97	Adult patients undergoing liver resection	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Operative blood loss (mL)	WMD -436 (-874, 1.67)	*No difference* 0.051	*NA*
Other surgery									
Henry (2007)	Level I/II *Good/Poor*	1 RCT N=30	Adult patients undergoing orthognathic surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Postoperative blood loss (mL)	WMD -513 (-717, -309)	*Favours aprotinin* <0.001	*NA*
Henry (2007)	Level I/II Good/Fair	1 RCT N=24	Adult patients undergoing thoracic surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Intraoperative blood loss (mL)	WMD -532 (-863, -199)	*Favours aprotinin 0.0016*	*NA*
						Postoperative blood loss (mL)	WMD -441 (-786, -96)	*Favours aprotinin 0.012*	*NA*
Apostolakis (2008)	Level II *Fair*	1 RCT N=59	Adult patients undergoing thoracic surgery	Hospital – planned surgery Greece	Ultra-low-dose aprotinin (IV) vs placebo[m]	Day 1 postoperative thoracic drainage (mL)	413 ± 199 vs 764 ± 214	*Favours aprotinin <0.001*	*NA*
						Day 2 postoperative thoracic drainage (mL)	248 ± 179 vs 455 ± 275	*Favours aprotinin 0.001*	*NA*
Henry (2007)	Level II *Good/Good*	1 RCT N=50	Adult patients undergoing vascular surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Postoperative blood loss (mL)	WMD -203 (-405, -1.07)	*Favours aprotinin* 0.049	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (mean ± SD) vs control (mean ± SD)	*Significance* P-value	
Leijdekkers (2006)	Level II *Fair*	1 RCT N=35	Adult patients undergoing surgery for infra-renal abdominal aneurysm	Hospital – planned surgery The Netherlands	Aprotinin (IV) vs placebo	Mean blood loss (mL)	2362 ± 1340 vs 2466 ± 1370	*No difference* 0.88	*NA*
PAEDIATRIC POPULATION/IV APROTININ									
Orthopaedic surgery									
Schouten (2009)	Level II *Fair*	1 RCT N=44	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs no aprotinin	Blood loss (mL)	WMD -385 (-727, -42)	*Favours aprotinin* NR	*NA*
Tzortzopoulou (2008)	Level I *Good*	2 RCTs N=87	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Blood loss (mL)	WMD -450 (-726, -174)	*Favours aprotinin* 0.0014	*None* P*het*=0.53 (I^2=0%)
ADULT POPULATION/TOPICAL APROTININ									
Cardiac surgery									
Abrishami (2009)	Level I *Good*	5 RCTs N=324	Adult patients undergoing primary on-pump cardiac surgery	Hospital – planned surgery Unknown	Aprotinin (topical) vs placebo	24-hr postoperative chest tube blood loss (mL)	WMD -204 (-276, -132)	*Favours aprotinin* <0.001	*Substantial* Phet=0.04 (I^2=60%)
Mehraien (2009)	Level II Good	1 RCT N=128	Adult patients undergoing first-time CABG (all patients)	Hospital – planned surgery Iran	Aprotinin (topical) vs placebo	24-hr postoperative chest tube blood loss (mL)	451 ± 218 vs 707 ± 269	*Favours aprotinin* 0.003	

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; mL, millilitres; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SMD, standardised mean difference; WMD, weighted mean difference.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] Prime' dose included regimens that added aprotinin to the pump prime solution of the cardiopulmonary bypass exclusively. 12/16 trials studied a 'prime' dose pf 2 million KIU, 2/16 trials studied a 'prime' dose of 1 million KIU, 1/16 trials studied a 'prime' dose of 500,000 KIU and 1/16 trials studies a 'prime' dose of 25,000 KIU/kg.
[e] Low-dose aprotinin was defined as any regimen that did not follow the 'full Hammersmith' regimen, including those studies that described their regimen as 'half Hammersmith'. For non-cardiac surgery trials, regimens were classified as low dose if the total dose was < 5 million KIU or 700 mg aprotinin.
[f] High-dose aprotinin was defined as any regimen that was described as the 'full Hammersmith' regimen. For non-cardiac surgery trials, regimens were classified as high-dose if the total dose was ≥ 5 million KIU or 700 mg aprotinin.
[g] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.
[h] Low dose (half-dose) aprotinin consisted of a 1 million KIU IV loading dose, 1 million KIU pump-priming dose, and 0.25 million KIU IV/h maintenance dose.
[i] Patients with peak aprotinin levels > 271 KIU/mL.
[j] Patients with peak aprotinin levels < 271 KIU/mL.
[k] Low dose aprotinin consisted of 1 million KIU infused over 30 min followed by a continuous infusion of 0/5 million KIU/h until the end of surgery.
[l] Total bleeding measured intraoperatively by weighing surgical sponges, postoperatively through drainage or perioperatively through the haemoglobin balance method which measures loss through comparison of pre- and postoperative haemoglobin concentrations (haematoma volumes as well as hidden or internal blood loss were excluded).
[m] Ultra-low dose aprotinin defined as a test dose of 1mL at intubation, followed by 0.5 million IU over 15 min following intubation, and again following closure.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on mortality?		Evidence table ref[a]: POQ3.I8a.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from up to 37 RCTs (31 RCTs for cardiac surgery), two supportive level I studies (Henry 2009/good quality; Brown 2007/fair quality), one supportive Level I/II study[b] (Gurusamy 2009/good-fair quality) and five additional RCTs (Grant 2008/fair quality; Later 2009/good quality; Colwell 2007/good quality; Apostolakis 2008/fair quality; Leijdekkers 2006/fair quality) which were published after the Henry 2007 review and were not included in the supportive reviews.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results mostly consistent between pivotal and supportive meta-analyses. Consistency of individual studies within the pivotal meta-analysis described below. Some difference between high and low dose aprotinin in Brown 2007. Additional RCTs consistent. Pivotal evidence – Henry 2007 No heterogeneity between studies. Supportive evidence - see Summary Table POQ3.I8a.P4	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 add percentages Any surgery – RR 0.90 (0.67, 1.20); 2.4% vs 2.6%; 37 RCTs (N=6645) Cardiac surgery – RR 0.95 (0.70, 1.28); 2.5% vs 2.4%; 31 RCTs (N=6058) Supportive evidence – Brown 2007 (for others see Summary Table POQ3.I8a.P4) Cardiac surgery (high dose) – RR 0.89 (0.65, 1.21); 43 RCTs (N=6175) Cardiac surgery (low dose) – RR 1.37 (0.72, 2.59); 14 RCTs (N=786)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis, although most were conducted in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

Mortality was underpowered in the individual studies but the Henry 2007 review included 6645 patients in total. Results from Brown 2007 shows a slight difference in direction of effect depending on dose (ie, high or low).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), two supportive level I studies, one supportive Level I/II study[b] and five additional RCTs.
2. Consistency	C	There was no heterogeneity in the pivotal level I evidence. Most additional studies were consistent. There was some difference in the direction of effect due to dose in one of the supportive level I studies.
3. Clinical impact	D	While there is no significant difference in mortality between intravenous aprotinin therapy and no therapy, and the risk estimates suggest no increased risk, the findings are uncertain due to underpowering.
4. Generalisability	B	The results are generalisable to an cardiac adult surgical population; most studies were conducted in cardiac surgery.
5. Applicability	B	Overall there were a large number of studies conducted in a wide range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of intravenous aprotinin therapy on mortality, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[b] A Level I/II study is a systematic review which includes only one RCT.

POQ3.I8a.P4 Characteristics and results of studies examining the effect of aprotinin on mortality

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	37 RCTs N=6645	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Mortality	RR 0.90 (0.67, 1.20)	*No difference* 0.47	*None* P*het*=0.95 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	31 RCTs N=6058	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Mortality	RR 0.95 (0.70, 1.28)	*No difference* 0.72	*None* P*het*=0.93 (I^2=0%)
Henry (2009)	Level I *Good*	32 RCTs N=6279	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs placebo	Mortality	RR 0.93 (0.69, 1.25)	*No difference* NR	*NR*
Brown (2007)	Level I *Fair*	43 RCTs N=6175	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	High dose aprotinin (IV) vs placebo[d]	Mortality	RR 0.89 (0.65, 1.21)	*No difference* 0.46	*NR*
		14 RCTs N=1453	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Low dose aprotinin (IV) vs placebo[e]	Mortality	RR 1.37 (0.72, 2.59)	*No difference* 0.34	*NR*
Grant (2008)	Level II *Fair*	1 RCT N=120	Adult patients undergoing off-pump coronary artery bypass surgery	Hospital – planned surgery US	Aprotinin (IV) vs placebo	1-year mortality	5.1% vs 13.1%	*No difference* NS	*NA*
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- to intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High dose aprotinin (IV) vs placebo[d]	In-hospital mortality	2.1% vs 1.0%	*No difference* 0.61	*NA*
Orthopaedic surgery									
Colwell (2007)	Level II *Good*	1 RCT N=352	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Mortality (up to 6 weeks)	0% vs 0.6%	No difference NS	*NA*
Liver surgery									
Gurusamy (2009)	Level I/II *Good/Fair*	1 RCT N=37	Adult patients undergoing liver resection	Hospital – planned surgery Unknown	Aprotinin (IV) vs placebo	Mortality	RR 1.18 (0.18, 7.48)	*No difference* 0.86	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity[b]*
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
Other surgery									
Apostolakis (2008)	Level II *Fair*	1 RCT N=59	Adult patients undergoing thoracic surgery	Hospital – planned surgery Greece	Ultra-low-dose aprotinin (IV) vs placebo[f]	In-hospital mortality	0% vs 0%	*No difference* NA	*NA*
Leijdekkers (2006)	Level II Fair	1 RCT N=35	Adult patients undergoing surgery for infra-renal abdominal aneurysm	Hospital – planned surgery The Netherlands	Aprotinin (IV) vs placebo	In-hospital mortality	6.3% vs 5.3%	*No difference* 1.00	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.
[e] Low dose (half-dose) aprotinin consisted of a 1 million KIU IV loading dose, 1 million KIU pump-priming dose, and 0.25 million KIU IV/h maintenance dose.
[f] Ultra-low dose aprotinin defined as a test dose of 1mL at intubation, followed by 0.5 million IU over 15 min following intubation, and again following closure.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on morbidity (coronary artery graft occlusion)?		Evidence table ref[a]: POQ3.I8a.P5 (CAGO)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes 2 RCTs, and one additional RCT (Grant 2008/fair quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Pivotal evidence – Henry 2007 Significant heterogeneity between two included studies (I^2=56%). Supportive evidence – Grant 2008 Additional RCT results consistent with one of the RCTs included in the Henry review.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Cardiac surgery – RR 0.76 (0.10, 5.67); 2 RCTs (N=728) Supportive evidence – Grant 2008 Off-pump CABG surgery (saphenous vein grafts) – 3.8% vs 8.9%; 1 RCT (N=120)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered/inconsistent
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned coronary artery bypass surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. There was one large multinational trial and one small US trial included in the pivotal level I study. The additional RCT was conducted in the US. The evidence may be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

CAGO not specifically defined in Henry review. CRG concerned regarding definition of CAGO in individual studies. The results of the pivotal review showed substantial heterogeneity and wide confidence intervals; therefore, the effect of aprotinin therapy on CAGO was considered uncertain.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality) which includes 2 RCTs, and one additional RCT.
2. Consistency	C	The results of the two trials included in the pivotal level I study were inconsistent. Additional RCT results consistent with one small RCT included in the pivotal level I study.
3. Clinical impact	D	While there is no significant difference in coronary artery graft occlusion between intravenous aprotinin therapy and no therapy, the findings are uncertain due to inconsistency and underpowering.
4. Generalisability	A	The results are generalisable to an adult population undergoing coronary artery bypass graft.
5. Applicability	C	There was one large multinational trial and one small US trial included in the pivotal level I study. The additional RCT was conducted in the US. The evidence may be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing coronary artery bypass surgery, the effect of intravenous aprotinin therapy on coronary artery graft occlusion, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.P5 (CAGO) Characteristics and results of studies examining the effect of aprotinin on morbidity (coronary artery graft occlusion)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* p-value	
ADULT POPULATION/IV APROTININ									
Cardiac surgery									
Henry (2007)	Level I *Good*	2 RCTs N=728	Adult patients undergoing cardiac surgery	Hospital – planned surgery Multinational and US	Aprotinin (IV) vs no aprotinin	Coronary artery graft occlusion	RR 0.76 (0.10, 5.67)	*No difference* 0.79	*Substantial* P*het*=0.13 (I^2=56%)
Grant (2008)	Level II Fair	1 RCT N=120	Adult patients undergoing off-pump coronary artery bypass surgery	Hospital – planned surgery US	Aprotinin (IV) vs placebo	6-month acute occlusion	3.8% vs 8.9% (SVGs)	*No difference NS*	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NA, not applicable; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio; SVG, saphenous vein graft.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on morbidity (myocardial infarction)?			Evidence table ref[a]: POQ3.I8a.P5 (MI)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
There is one pivotal Level I study (Henry 2007/good quality), which included data from 34 RCTs (31 RCTs for cardiac surgery), one supportive level I study (Brown 2007/fair quality) and four additional RCTs, three in cardiac surgery (Grant 2008/fair quality; Later 2009/good quality/Nurözler 2008/fair quality) and one in hip replacement surgery(Colwell 2007/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Results consistent between Henry and Brown reviews. However, a slight difference in direction of the point estimate by dose was seen in the Brown review. Additional RCTs consistent. Pivotal evidence – Henry 2007 No heterogeneity between studies.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Pivotal evidence – Henry 2007 Any surgery – RR 0.92 (0.72, 1.18); 4.3% vs 4.6%; 34 RCTs (N=5758) Cardiac surgery – RR 0.95 (0.74, 1.22); 4.7% vs 4.7%; 31 RCTs (N=5279) Supportive evidence – Brown 2007 (see also Supportive Table POQ3.18a.P5(MI)) Cardiac surgery (high dose) – RR 1.10 (0.83, 1.45); 31 RCTs (N=3315) Cardiac surgery (low dose) – RR 0.94 (0.58, 1.54); 16 RCTs (N=1585)	A	Very large	
	B	Substantial	
	C	Moderate	
	D	No difference	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The evidence is generalisable primarily to an adult population who are undergoing planned cardiac surgery; 31/34 studies included in the pivotal review were conducted in cardiac surgery, as were 3/4 RCTs. 1 recent RCT provides data on hip replacement surgery.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Hospital setting. There are a large number of RCTs in the Henry review from a wide range of countries. It is unclear where these studies were conducted. The one additional recent RCT in hip replacement surgery was conducted in the US and Canada.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

MI had a higher incidence than mortality (~ 4% in Henry 2007), so the results presented in the Henry review for MI are more likely to be adequately powered than they were for mortality. Also had narrower confidence intervals than mortality. CRG concerned regarding the definition of MI in the individual included studies.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive level I study and four additional RCTs (three in cardiac surgery and one in hip replacement surgery).
2. Consistency	B	There was no heterogeneity in the pivotal level I evidence. Most additional studies were consistent. There was a slight difference in the direction of effect due to dose in the supportive level I studies.
3. Clinical impact	D	For cardiac surgery, there is no significant difference in the risk of myocardial infarction between intravenous aprotinin therapy and no therapy. For hip replacement surgery there was only RCT which was underpowered to detect a difference.
4. Generalisability	B	The results are generalisable primarily to cardiac surgery. There was also a recent RCT in hip replacement surgery.
5. Applicability	B	Studies were conducted in a wide range of countries. Likely to be applicable to the Australian setting. The single included RCT in hip replacement surgery was conducted in the US and Canada. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above

In adult patients undergoing cardiac surgery, intravenous aprotinin therapy does not appear to have an effect on the risk of myocardial infarction compared with no therapy.

In adult patients undergoing hip replacement surgery, the effect of intravenous aprotinin therapy on the risk of myocardial infarction, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.P5 (MI) Characteristics and results of studies examining the effect of aprotinin on morbidity (myocardial infarction)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	34 RCTs N=5758	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Myocardial infarction	RR 0.92 (0.72, 1.18)	*No difference* 0.50	*None* P*het*=0.91 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	31 RCTs N=5279	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Myocardial infarction	RR 0.95 (0.74, 1.22)	*No difference* 0.69	*None* P*het*=0.92 (I^2=0%)
Henry (2009)	Level 1 *Good*	34 RCTs N=5441	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs placebo	Myocardial infarction	RR 0.94 (0.73, 1.21)	*No difference* NR	*NR*
Brown (2007)	Level I *Fair*	31 RCTs N=3315	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	High dose aprotinin (IV) vs placebo[d]	Myocardial infarction	RR 1.10 (0.83, 1.45)	*No difference* 0.52	*NR*
		16 RCTs N=1585	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Low dose aprotinin (IV) vs placebo[e]	Myocardial infarction	RR 0.94 (0.58, 1.54)	*No difference* 0.82	*NR*
Grant (2008)	Level II *Fair*	1 RCT N=120	Adult patients undergoing off-pump coronary artery bypass surgery	Hospital – planned surgery US	Aprotinin (IV) vs placebo	In-hospital myocardial infarction	1.7% vs 6.6%	*No difference* NS	*NA*
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- to intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High dose aprotinin (IV) vs placebo[d]	Perioperative myocardial infarction	1.0% vs 7.8%	Favours aprotinin 0.023	*NA*
Nurözler (2008)	Level II *Fair*	1 RCT N=51	Adult patients undergoing off-pump coronary bypass who have received clopidogrel within 5 days of surgery (all patients)	Hospital – planned surgery Turkey	Low-dose aprotinin (IV) vs placebo[f]	Myocardial infarction	0% vs 0%	*No difference* NA	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
Orthopaedic surgery									
Colwell (2007)	Level II *Good*	1 RCT N=352	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Myocardial infarction	0.6% vs 0.6%	No difference NS	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; *het*, heterogeneity; IV, intravenous; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.
[e] Low dose (half-dose) aprotinin consisted of a 1 million KIU IV loading dose, 1 million KIU pump-priming dose, and 0.25 million KIU IV/h maintenance dose.
[f] Low dose aprotinin consisted of 1 million KIU infused over 30 min followed by a continuous infusion of 0/5 million KIU/h until the end of surgery.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on morbidity (renal failure/dysfunction)?		Evidence table ref[a]: POQ3.I8a.P5 (renal)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which included data from 14 RCTs (11 RCTs for cardiac surgery) , one supportive level I study (Brown 2007/fair quality) and three additional RCTs (Grant 2008/fair quality; Later 2009/good quality; Colwell 2007/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results mostly consistent between the Henry and Brown reviews. However, significant renal dysfunction was seen for high dose aprotinin in Brown review. Most additional RCTs consistent, although Later 2009 showed less renal complications in aprotinin arm. Pivotal evidence – Henry 2007 No heterogeneity between studies.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (renal failure/dysfunction) – RR 1.16 (0.79, 1.70); 3.0% vs 2.2%; 14 RCTs (N=3908) Cardiac surgery (renal failure/dysfunction) – RR 1.12 (0.74, 1.67); 2.9% vs 2.2%; 11 RCTS (N=3670) Supportive evidence – Brown 2007 (see also Supportive Table POQ3.I8a.P5(renal) Cardiac surgery (renal failure; high dose) – RR 1.09 (0.68, 1.77); 27 RCTs (N=4681) Cardiac surgery (renal dysfunction; high dose) – RR 1.47 (1.12, 1.94); 19 RCTs (N=1778)	A	Very large
	B	Substantial
	C	Moderate (renal dysfunction)
	D	Slight (renal failure)
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. 11/14 studies included in the pivotal review were conducted in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. Studies conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

CRG noted that eGFR calculation is not a good measure and only to be used in stable patients, not post-surgery. Grant used CT angiography with 100-150 mL contrast which may explain if baseline levels were high. Varying definitions between studies; some renal endpoints were soft.

Later 2009 RCT defined outcomes as follows: Renal failure as defined by Mangano (2006): required a postoperative serum creatinine of at least 2.0 mg/dL with an increase over the preoperative baseline level of at least 0.7 mg/dL; renal complication as defined by the RIFLE classification: risk of renal dysfunction defined as a 1.5 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 6 hours. Kidney injury was defined as a 2 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 12 hours, whilst renal failure was defined as a 3 times increase in perioperative creatinine plasma concentration or a urine output < 0.3 mL/kg/h in 24 hours.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating		Description
	Renal failure	Renal dysfunction	
1. Evidence base	A	A	There is one pivotal Level I (good quality) study, one supportive level I study and three additional RCTs.
2. Consistency	C	C	There is some inconsistency regarding dose in the supportive level I study and for renal dysfunction/complications which may be due to the definitions used in different studies.
3. Clinical impact	D	C	There was no significant difference between intravenous aprotinin therapy and no therapy for renal failure. There were inconsistent results on the basis of dose for renal dysfunction/complications (C for dysfunction, D for failure).
4. Generalisability	C	C	The results are generalisable to an adult surgical population but most studies were in cardiac surgery.
5. Applicability	B	B	Overall there were a large number of studies conducted in a wide range of countries. Additional individual RCTs were conducted in the US, Canada and the Netherlands. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy does not appear to affect the risk of postoperative renal failure, compared with no therapy, but may impair postoperative renal function.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.P5 (renal) Characteristics and results of studies examining the effect of aprotinin on morbidity (renal failure/dysfunction)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	14 RCTs N=3908	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Renal failure/dysfunction	RR 1.16 (0.79, 1.70)	*No difference* 0.46	*None* P*het*=0.88 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	11 RCTs N=3670	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Renal failure/dysfunction	RR 1.12 (0.74, 1.67)	*No difference* 0.60	*None* P*het*=0.85 (I^2=0%)
Brown (2007)	Level I Fair	27 RCTs N=4681	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	High dose aprotinin (IV) vs placebo[d]	Renal failure[e]	RR 1.09 (0.68, 1.77)	*No difference* 0.71	*NR*
		7 RCTs N=786	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Low dose aprotinin (IV) vs placebo[f]	Renal failure[e]	RR 1.86 (0.07, 49.26)	*No difference* 0.71	*NR*
Brown (2007)	Level I *Fair*	19 RCTs N=1778	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	High dose aprotinin (IV) vs placebo[d]	Renal dysfunction[g]	RR 1.47 (1.12, 1.94)	*Favours no aprotinin* 0.006	*NR*
		9 RCTs N=1041	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Low dose aprotinin (IV) vs placebo[f]	Renal dysfunction[g]	RR 1.01 (0.69, 1.49)	*No difference* 0.961	*NR*
Grant (2008)	Level II *Fair*	1 RCT N=120	Adult patients undergoing off-pump coronary artery bypass surgery	Hospital – planned surgery US	Aprotinin (IV) vs placebo	Acute renal failure within 6 months[h]	3.4% vs 3.3%	*No difference* NS	*NA*
						Postoperative acute kidney injury[i]	45.8 vs 24.6	*Favours no aprotinin* <0.03	*NA*
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- to intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High dose aprotinin (IV) vs placebo[d]	Renal failure[j]	3.1% vs 2.9%	*No difference* 1.0	*NA*
						Renal complication[k]	10.4% vs 17.5%	*Favours aprotinin* 0.011	NA

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or AP (%) vs control (%)	*Significance* P-value	
Orthopaedic surgery									
Colwell (2007)	Level II *Good*	1 RCT N=352	Adults undergoing unilateral total hip arthroplasty (all patients)	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Renal failure (not defined)	1.1% vs 1.1%	No difference NS	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; *het*, heterogeneity; IV, intravenous; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.
[e] Renal failure defined as a new onset of dialysis except in one study where it was defined as a ≥ 2 mg/dL creatinine level.
[f] Low dose (half-dose) aprotinin consisted of a 1 million KIU IV loading dose, 1 million KIU pump-priming dose, and 0.25 million KIU IV/h maintenance dose.
[g] Renal dysfunction defined as a ≥ 0.5 mg/dL increase in creatinine.
[h] Acute renal failure defined as postoperative eGFR < 75% of baseline and urine output is < 0.5 mL/kg/h for 6 hours.
[i] Postoperative kidney injury defined as postoperative eGFR < 75% of baseline.
[j] Renal failure as defined by Mangano (2006)[1]. Required a postoperative serum creatinine of at least 2.0 mg/dL with an increase over the preoperative baseline level of at least 0.7 mg/dL.
[k] Renal complication as defined by the RIFLE classification[2]. Risk of renal dysfunction defined as a 1.5 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 6 hours. Kidney injury was defined as a 2 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 12 hours, whilst renal failure was defined as a 3 times increase in perioperative creatinine plasma concentration or a urine output < 0.3 mL/kg/h in 24 hours.
[l] Renal complication defined as serum creatinine > 3.5 mg/dL or 309 µmol/L.

[1] Mangano et al (2006) The risk associated with aprotinin in cardiac surgery. NEJM 354:353-365.
[2] Kuitunen et al (2006) Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. Ann Thorac Surg 81: 542-546.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on morbidity (stroke)?		Evidence table ref[a]: POQ3.I8a.P5 (stroke)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from 14 RCTs (9 in cardiac surgery), one supportive level I study (Brown 2007/fair quality) and two additional RCTs (Later 2009/good quality; Nurözler 2008/fair quality) published after the Henry 2007 review.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between Henry and Brown reviews. Additional RCTs consistent. Pivotal evidence – Henry 2007 No heterogeneity between studies.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – RR 0.78 (0.38, 1.62); 1.1% vs 1.7%; 14 RCTs (N=2158) Cardiac surgery – RR 0.76 (0.30, 1.93); 1.3% vs 1.9%; 9 RCTs (N=1163) Supportive evidence – Brown 2007 (see also Supportive Table POQ3.I8a.P5 (stroke)) Cardiac surgery (high dose) – RR 0.67 (0.30, 1.47); 22 RCTs (N=1737) Cardiac surgery (low dose) – RR 0.47 (0.09, 2.36); 10 RCTs (N=1049)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery; 9/14 studies included in the Henry review were conducted in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. Studies conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is an antifibrinolytic agent. In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

Studies underpowered for this outcome. Only one RCT showed a slight difference but this was based on a very small sample size (ie, only one patient in the aprotinin arm had a stroke).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive level I study and two additional RCTs.
2. Consistency	A	There was no heterogeneity in the pivotal level I study. Results of the supportive level I study and additional RCTs consistent with pivotal evidence.
3. Clinical impact	D	Results show no significant difference but studies likely to be underpowered to detect a difference in stroke.
4. Generalisability	B	The results are generalisable to an adult surgical population; more than half of studies were in cardiac surgery.
5. Applicability	B	Overall there were a large number of studies conducted in a wide range of countries. The additional RCTs were conducted in Turkey and the Netherlands. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous aprotinin therapy on the risk of stroke, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.P5 (stroke) Characteristics and results of studies examining the effect of aprotinin on morbidity (stroke)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	14 RCTs N=2158	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Stroke	RR 0.78 (0.38, 1.62)	*No difference* 0.51	*None* P*het*=0.71 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	9 RCTs N=1163	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Stroke	RR 0.76 (0.30, 1.93)	*No difference* 0.57	*None* P*het*=0.40 (I^2=4%)
Brown (2007)	Level I *Fair*	22 RCTs N=1737	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	High dose aprotinin (IV) vs placebo[d]	Stroke	RR 0.67 (0.30, 1.47)	*No difference* 0.32	*NR*
	Level I *Fair*	10 RCTs N=1049	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Low dose aprotinin (IV) vs placebo[e]	Stroke	RR 0.47 (0.09, 2.36)	*No difference* 0.36	*NR*
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- to intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High dose aprotinin (IV) vs placebo[d]	Stroke	1.0% vs 1.0%	*No difference* 1.0	NA
Nurözler (2008)	Level II *Fair*	1 RCT N=51	Adult patients undergoing off-pump coronary bypass who have received clopidogrel within 5 days of surgery (all patients)	Hospital – planned surgery Turkey	Low-dose aprotinin (IV) vs placebo[f]	Stroke	4% vs 0%	*No difference* 0.317	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.
[e] Low dose (half-dose) aprotinin consisted of a 1 million KIU IV loading dose, 1 million KIU pump-priming dose, and 0.25 million KIU IV/h maintenance dose.
[f] Low dose aprotinin consisted of 1 million KIU infused over 30 min followed by a continuous infusion of 0/5 million KIU/h until the end of surgery.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on morbidity (thrombosis)?		Evidence table ref[a]: POQ3.I8a.P5 (thromb)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which included up to 11 RCTs (depending on the specific outcome examined), three supportive level I studies (Kagoma 2009/good quality; Liu 2008/poor quality; McIlroy 2009/good quality) and one additional RCT (Colwell 2007/good quality) published since the Henry review.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Some inconsistency between results; may be due to different surgery types and specific thrombosis outcomes. Additional RCTs consistent. Pivotal evidence – Henry 2007 No heterogeneity between studies.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (DVT) – RR 0.79 (0.46, 1.34); 5.3% vs 5.4%; 11 RCTs (N=986) Cardiac surgery (DVT) – RR 2.52 (0.41, 15.45); 2.4% vs 1.0%; 2 RCTs (N=272) Any surgery (PE) – RR 1.98 (0.38, 10.46); 3.1% vs 1.9%; 2 RCTs (N=175) Other outcomes and supportive evidence-see Supportive Table POQ3.I8a.P5 (thrombosis)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered/inconsistent
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery; 2/11 studies included in the Henry review were conducted in cardiac surgery for DVT and 3/7 studies conducted in cardiac surgery for other thrombosis.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. Studies conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

CRG noted that variations in definition and how measured may make a difference. Included studies underpowered to detect these outcomes.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), three supportive level I studies and one additional RCT.
2. Consistency	C	There was no heterogeneity in the pivotal level I study for each thrombosis outcome (DVT, PE, other thrombosis). Results of the supportive level I studies and additional RCT showed some inconsistency, possibly due to different surgeries and definitions of thrombosis outcomes.
3. Clinical impact	D	There was no significant difference in any results but some of the risk estimates were large. Likely to be underpowered for thrombosis outcomes.
4. Generalisability	B	The results are generalisable to an adult surgical population.
5. Applicability	B	Overall there were a reasonable number of studies conducted in a range of countries. The additional RCT was conducted in the US/Canada. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous aprotinin therapy on the risk of venous thromboembolism, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.P5 (thrombosis) Characteristics and results of studies examining the effect of aprotinin on morbidity (thrombosis)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	11 RCTs N=986	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Deep vein thrombosis	RR 0.79 (0.46, 1.34)	*No difference* 0.38	*None* P*het*=0.80 (I^2=0%)
Henry (2007)	Level I *Good*	2 RCTs N=175	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Pulmonary embolism	RR 1.98 (0.38, 10.46)	*No difference* 0.42	*None* P*het*=0.95 (I^2=0%)
Henry (2007)	Level I *Good*	7 RCTs N=583	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Other thrombosis (not MI, stroke, DVT or PE)	RR 0.73 (0.25, 2.15)	*No difference* 0.57	*None* P*het*=0.64 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	2 RCTs N=272	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Deep vein thrombosis	RR 2.52 (0.41, 15.45)	*No difference* 0.32	*None* P*het*=0.71 (I^2=0%)
Henry (2007)	Level I *Good*	3 RCTs N=370	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Aprotinin (IV) vs no aprotinin	Other thrombosis (not MI, stroke, DVT or PE)	RR 0.62 (0.11, 3.36)	*No difference* 0.58	*None* P*het*=0.50 (I^2=0%)
McIlroy (2009)	Level I Good	3 RCTs N=174	Adult patients receiving aspirin undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Aprotinin (IV) vs placebo	Thrombotic complication (includes DVT, stroke, MI or PE)	OR 0.51 (0.21, 1.20)	*No difference 0.12*	*None Phet=0.76 (I2=0%)*
Orthopaedic surgery									
Kagoma (2009)	Level I *Good*	3 trials N=97	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Countries not specified	Aprotinin (IV) vs placebo	Venous thromboembolism (including DVT and PE)	RD -0.04 (-0.09, 0.02)	*No difference* NR	*NR*
Colwell (2007)	Level II *Good*	1 RCT N=352	Adults undergoing unilateral total hip arthroplasty	Hospital – planned surgery US/Canada	Aprotinin (IV) vs placebo	Deep vein thrombosis	1.1% vs 1.7%	No difference NS	*NA*
						Pulmonary embolism	1.1% vs 1.1%	No difference NS	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
Liver surgery									
Liu (2008)	Level I *Poor*	2 RCTs N=200	Adult patients undergoing orthotopic liver transplantation	Hospital – planned surgery Countries not specified	Aprotinin (IV) vs no aprotinin	Thromboembolic events (not defined)	OR 0.38 (0.09, 1.64)	*No difference* >0.05	*None* P*het*=0.88

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NA, not applicable; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on quality of life?		Evidence table ref[a]: POQ3.I8a.P6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies of any level were identified which assessed the effect of tranexamic acid on quality of life.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous aprotinin therapy on quality of life, compared with no therapy, is unknown.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on re-operation for bleeding?		Evidence table ref[a]: POQ3.I8a.S2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which included data from 36 RCTs (33 RCTs for cardiac surgery), three supportive level I studies (Henry 2009/good quality; Brown 2007/fair quality; McIlroy 2009/good quality) and four additional RCTs (Later 2009/good quality; Nurözler 2008/fair quality; Apostolakis 2008/fair quality; Leijdekkers 2006/fair quality) published following the Henry review .	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive studies. Additional RCTs consistent. Pivotal evidence – Henry 2007 No heterogeneity between studies.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 (re-operation for bleeding) Any surgery – RR 0.48 (0.35, 0.68); 1.9% vs 4.7%; 36 RCTs (N=4715) Cardiac surgery – RR 0.49 (0.34, 0.70); 1.9% vs 4.5%; 33 RCTs (N=4534) Supportive evidence – Brown 2007 (return to operating room) – see also Supportive Table POQ3.I8a.S2 Cardiac surgery (high dose) – RR 0.47 (0.32, 0.69); 49 RCTs (N=3912) Cardiac surgery (low dose) – RR 0.69 (0.41, 1.18); 20 RCTs (N=1623)	A	Very large
	B	Substantial (cardiac)
	C	Moderate
	D	Underpowered (non-cardiac)
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery; 33/36 studies included in Henry 2007 conducted in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. Studies conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

Later 2009 study presented results for re-operation due to surgical bleeding and re-operation due to non-surgical bleeding. When these are combined to include re-operation due to any bleeding, there is no difference between arms. Differences due to dose in Brown 2007 study. Low dose category may be underpowered, thus more uncertainty.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating		Description
	Cardiac	Non-cardiac	
1. Evidence base	A	A	There is one pivotal Level I (good quality) study, three supportive level I studies and four additional RCTs.
2. Consistency	B	B	There was no heterogeneity in the pivotal level I study. There was some inconsistency for reoperation (not defined) due to dose in one of the supportive level I studies. The results for cardiac surgery were largely consistent.
3. Clinical impact	B	D	For cardiac surgery, there were significantly less re-operations due to bleeding in patients receiving aprotinin therapy compared with no therapy. For non-cardiac surgery, the results were likely underpowered.
4. Generalisability	B	B	The results are generalisable to an adult surgical population; most studies in cardiac surgery.
5. Applicability	B	B	Overall there were a large number of studies conducted in a wide range of countries. Additional RCTs conducted in the Netherlands, Turkey and Greece. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, intravenous aprotinin therapy reduces the risk of reoperation for bleeding compared with no therapy.

In adult patients undergoing noncardiac surgery, the effect of intravenous aprotinin therapy on reoperation for bleeding, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.S2 Characteristics and results of studies examining the effect of aprotinin on reoperation for bleeding

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	36 trials N=4715	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs placebo	Reoperation for bleeding	RR 0.48 (0.35, 0.68)	*Favours aprotinin* <0.001	*None* P*het*=0.51 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	33 RCTs N=4534	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs placebo	Reoperation for bleeding	RR 0.49 (0.34, 0.70)	*Favours aprotinin* <0.001	*None* P*het*=0.41 (I^2=4%)
Henry (2009)	Level I *Fair*	NR[d]	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs placebo	Reoperation for bleeding	RR 0.48 (0.34, 0.67)	*Favours aprotinin* NR	*NR*
Brown (2007)	Level I *Fair*	40 RCTs N=3912	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	High dose aprotinin (IV) vs placebo[e]	Return to operating room (reason/s not defined)	RR 0.47 (0.32, 0.69)	*Favours aprotinin* <0.001	*NR*
		20 RCTs N=1623	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Low dose aprotinin (IV) vs placebo[f]	Return to operating room (reason/s not defined)	RR 0.69 (0.41, 1.18)	*No difference* 0.176	*NR*
McIlroy (2009)	Level I *Good*	4 RCTs N=198	Adult patients receiving ASA undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Aprotinin (IV) vs placebo	Reoperation for bleeding	OR 0.42 (0.13, 1.36)	*No difference* 0.15	*None* P*het*=0.61 (I^2=0%)
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- to intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High dose aprotinin (IV) vs placebo[e]	Reoperation for any reason	5.2% vs 13.6%	*No difference* 0.054	*NA*
						Reoperation due to surgical bleeding	4.2% vs 2.9%	*No difference* 0.71	*NA*
						Reoperation due to non-surgical bleeding	0% vs 3.9%	*No difference* 0.12	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or Aprotinin (%) vs control (%)	*Significance* P-value	
Nurözler (2008)	Level II *Fair*	1 RCT N=51	Adult patients undergoing off-pump coronary bypass who have received clopidogrel within 5 days of surgery (all patients)	Hospital – planned surgery Turkey	Low-dose aprotinin (IV) vs placebo[g]	Reoperation for bleeding	0% vs 7.7%	*No difference* 0.157	*NA*
Other surgery									
Apostolakis (2008)	Level II *Fair*	1 RCT N=59	Adult population undergoing thoracic surgery	Hospital – planned surgery Greece	Ultra-low-dose aprotinin vs placebo[h]	Reoperation for bleeding	0% vs 0%	*No difference* NA	*NA*
Leijdekkers (2006)	Level II Fair	1 RCT N=35	Adult patients undergoing surgery for infra-renal abdominal aneurysm	Hospital – planned surgery The Netherlands	Aprotinin (IV) vs placebo	Reoperation for bleeding	6.3% vs 10.5%	*No difference* 0.65	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.

Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.

[d] Not specifically reported in the text of the publication.

[e] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.

[f] Low dose (half-dose) aprotinin consisted of a 1 million KIU IV loading dose, 1 million KIU pump-priming dose, and 0.25 million KIU IV/h maintenance dose.

[g] Low dose aprotinin consisted of 1 million KIU infused over 30 min followed by a continuous infusion of 0/5 million KIU/h until the end of surgery.

[h] Ultra-low dose aprotinin defined as a test dose of 1mL at intubation, followed by 0.5 million IU over 15 min following intubation, and again following closure.

Key question(s): In patients undergoing surgery, what is the effect of administration of aprotinin on hospital length of stay?		Evidence table ref[a]: POQ3.I8a.S5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from 21 RCTs (13 for cardiac surgery) and two additional RCTs (Later 2009/good quality; Nurözler 2008/fair quality) published after the Henry review.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Pivotal evidence – Henry 2007 Mild-moderate heterogeneity between studies. Additional RCTs consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – WMD -0.01 (-0.50, 0.48); 21 RCTs (N=1570) Cardiac surgery – WMD -0.10 (-0.64, 0.44); 13 RCTs (N=1412) Supportive evidence – see Supportive Table POQ3.I8a.S5	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery; 13/21 studies included in the Henry review conducted in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. Studies conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In 2007, Bayer announced a worldwide suspension of aprotinin supply due to the results of the BART trial which suggested increased risk of mortality for aprotinin compared with the lysine analogues tranexamic acid and ε-aminocaproic acid.

Differences of 1% of a day not considered by the CRG to be clinically important.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I (good quality) study and two additional RCTs.
2. Consistency	B	There was some heterogeneity in the pivotal level I (good quality) study. The results of the additional RCTs were consistent.
3. Clinical impact	D	There was no significant difference in hospital length of stay for intravenous aprotinin therapy compared with no therapy.
4. Generalisability	B	The results are generalisable to an adult surgical population.
5. Applicability	B	Studies were conducted in a wide range of countries. The additional RCTs were conducted in the Netherlands and Turkey. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy has no effect on hospital length of stay compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.S5 Characteristics and results of studies examining the effect of aprotinin on hospital length of stay

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) Or Aprotinin (Mean ± SD) vs control (mean ± SD)	*Significance* P-value	
ADULT POPULATION/IV APROTININ									
Any surgery									
Henry (2007)	Level I *Good*	21 trials N=1570	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Hospital length of stay (days)	WMD -0.01 (-0.50, 0.48)	*No difference* 0.96	*Mild* P*het*=0.19 (I^2=23%)
Cardiac surgery									
Henry (2007)	Level I *Good*	13 RCTs N=1412	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Aprotinin (IV) vs no aprotinin	Hospital length of stay (days)	WMD -0.10 (-0.64, 0.44)	*No difference* 0.73	*Moderate* P*het*=0.12 (I^2=33%)
Later (2009)	Level II *Good*	1 RCT N=199	Adult patients undergoing low- to intermediate-risk cardiac surgery	Hospital – planned surgery The Netherlands	High-dose aprotinin (IV) vs placebo[d]	Hospital length of stay (days)	7.8 ± 6.7 vs 8.5 ± 7.4	*No difference* 0.49	*NA*
Nurözler (2008)	Level II *Fair*	1 RCT N=51	Adult patients undergoing off-pump coronary bypass who have received clopidogrel within 5 days of surgery	Hospital – planned surgery Turkey	Low-dose aprotinin (IV) vs placebo[e]	Hospital length of stay (days)	5.3 ± 1.6 vs 5.5 ± 1.4	*No difference* 0.660	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] High dose (full-dose) aprotinin defined as a 2 million kallikrein-inhibiting units (KIU) IV loading dose, 2 million KIU pump-priming dose, and 0.5 million KIU IV/h maintenance dose.
[e] Low dose aprotinin consisted of 1 million KIU infused over 30 min followed by a continuous infusion of 0/5 million KIU/h until the end of surgery.

Recommendation(s) for administration of aprotinin

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
No recommendation made because the drug has been withdrawn due to concerns that it is less safe than alternative therapies.		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?	YES	NO

Intervention 8 – Administration of antifibrinolytics & DDAVP: Tranexamic acid

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on transfusion incidence?		Evidence table ref[a]: POQ3.I8b.P1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I (Henry 2007/good quality) which includes data from up to 51 RCTs, two supportive level I studies (Brown 2007/fair quality; Kagoma 2009/good quality), two supportive level I/II studies which include one RCT each (Kongnyuy 2009/good-good quality; McIlroy 2009/good-poor quality) and nine additional RCTs (Jimenez 2007/good quality; Later 2009/good quality; Mehr-Aein 2007/good quality; Taghaddomi 2009/fair quality; Alvarez 2008/fair quality; Elwatidy 2008/fair quality; Sadeghi 2007/good quality; Wong 2008/good quality; Choi 2009/fair quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results mostly consistent between pivotal and supportive meta-analyses and RCTs. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 Moderate to substantial heterogeneity (see note) in main analyses and most subgroup analyses. Differences may be due to different surgery types, and transfusion of different blood products.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – 27.0% vs 43.8%; RR 0.61 (0.54, 0.70); 51 RCTs (N=3751) Cardiac surgery – 27.8% vs 40.8%; RR 0.69 (0.60, 0.79); 28 RCTs (N=2443) Orthopaedic surgery – 26.7% vs 52.2%; RR 0.44 (0.33, 0.60); 20 RCTs (N=953) Liver surgery – 19.6% vs 36.5%; RR 0.16 (0.00, 32.47); 2 RCTs (N=296) Supportive evidence – see Summary Table POQ3.I8b.P1	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis. There were also analyses of patients undergoing cardiac surgery who had received ASA within 7 days prior to surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review included studies from a wide range of countries. Included RCTs were from a number of different countries including several from the Middle East and Asia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

The Henry (pivotal) review assessed quality and performed a subgroup analysis of transfusion incidence for all surgery types based on the rating (A,B or C) of treatment allocation[b]. The analysis showed no substantial difference in the results between studies rated A, B or C.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I (good quality), two supportive level I studies, two supportive level I/II studies and nine additional RCTs.
2. Consistency	B	Significant heterogeneity in the pivotal level I study but mostly due to difference in magnitude of effect and not direction of effect. Differences may be due to different surgery types. Results of supportive level I studies and additional RCTs consistent with pivotal evidence.
3. Clinical impact	B	There were significant differences between intravenous tranexamic acid therapy and no therapy overall and for surgery subgroups.
4. Generalisability	B	The results are generalisable to an adult surgical population undergoing cardiac, major joint and spinal surgery.
5. Applicability	B	Overall there were a large number of studies conducted in a wide range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery and major orthopaedic surgery, intravenous tranexamic acid therapy reduces the incidence of allogeneic blood transfusion compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: ASA, acetylsalicylic acid; RCT, randomised controlled trial; RR, risk ratio; SR, systematic review.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[b] Cochrane ratings defined as follows: Grade A, adequate allocation concealment; Grade B, uncertain allocation concealment; Grade C, inadequate allocation concealment.

POQ3.I8b.P1 Characteristics and results of studies examining the effect of tranexamic acid on transfusion incidence.

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	51 RCTs N=3751	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.61 (0.54, 0.70)	*Favours tranexamic acid* <0.001	*Substantial* P*het*<0.001 (I^2=50%)
Henry (2007)	Level I *Good*	45 RCTs N=3191	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid with transfusion protocol	Transfusion incidence (allogeneic blood)	RR 0.57 (0.49, 0.66)	*Favours tranexamic acid* <0.001	*Moderate* P*het*=0.001 (I^2=44%)
		6 RCTs N=560	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid without transfusion protocol	Transfusion incidence (allogeneic blood)	RR 0.82 (0.63, 1.07)	*No difference* 0.15	*Substantial* P*het*=0.02 (I^2=63%)
Henry (2007)	Level I *Good* Rating A[d]	21 RCTs N=1610	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.60 (0.49, 0.72)	*Favours tranexamic acid* <0.001	*Moderate* P*het*=0.02 (I^2=42%)
	Level I *Good* Rating B[d]	20 RCTs N=1254	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.55 (0.42, 0.73)	*Favours tranexamic acid* <0.001	*Substantial* P*het*<0.001 (I^2=62%)
	Level I *Good* Rating C[d]	10 RCTs N=927	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.69 (0.56, 0.86)	*Favours tranexamic acid* 0.0012	*Moderate* P*het*=0.09 (I^2=40%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
Cardiac surgery									
Henry (2007)	Level I *Good*	28 RCTs N=2443	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.69 (0.60, 0.79)	*Favours tranexamic acid* <0.001	*Moderate* P*het*=0.03 (I^2=37%)
		16 RCTs N=926	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid total dose < 2.0 g (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.72 (0.59, 0.88)	*Favours tranexamic acid 0.0013*	*Moderate* P*het*=0.05 (I^2=40%)
		13 RCTs N=1571	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid total dose 2.0 – 10.0 g (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.67 (0.55, 0.83)	*Favours tranexamic acid* <0.001	*Moderate* P*het*=0.09 (I^2=37%)
Henry (2009)	Level I *Good*	N RCTs NR N=NR	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.70 (0.61, 0.80)	*Favours tranexamic acid* NR	*NR*
Brown (2007)	Level I *Fair*	22 RCTs N=2429	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Transfusion incidence (pRBCs)	RR 0.75 (0.60, 0.92)	*Favours tranexamic acid* 0.007	*NR*
McIlroy (2009)	Level I/II *Good/Poor*	1 RCT N=79	Adult patients receiving aspirin undergoing CABG surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Transfusion incidence (allogeneic blood products)	RR 0.97 (0.32, 2.90)	*No difference* 0.95	*NA*
Jimenez (2007)	Level II *Good*	1 RCT N=50	Adults undergoing cardiopulmonary bypass surgery	Hospital - planned surgery Spain	Tranexamic acid (IV) vs placebo	Transfusion incidence (RBC and plasma/0-4 hr)	4.2% vs 7.6%	*No difference* 0.39	*NA*
						Transfusion incidence (RBC and plasma/chest tube withdrawal)	37.5% vs 73.1%	*Favours tranexamic acid* 0.01	*NA*
						Transfusion incidence (plasma/chest tube withdrawal)	4.2% vs 30.8%	*Favours tranexamic acid* 0.02	*NA*
Later (2009)	Level II *Good*	1 RCT N=202	Adults undergoing first-time, non-complex cardiac surgery with CPB	Hospital - planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Transfusion incidence (pRBC)	57.6% vs 70.9%	*No difference* 0.057	*NA*
						Transfusion incidence (blood products)	69.7% vs 78.6%	*No difference* 0.15	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adults undergoing off-pump CABG surgery	Hospital - planned surgery	Tranexamic acid (IV) vs placebo	Transfusion incidence (whole blood or pRBC)	15.2% vs 24.2%	*No difference* 0.07	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
				Iran		Transfusion incidence (FFP)	0% vs 18.2%	*No difference* 0.05	*NA*
						Transfusion incidence (platelets)	0% vs 0%	*No difference* NA	*NA*
						Transfusion incidence (any blood products)	15.2% vs 36.4%	*No difference* 0.09	*NA*
Taghaddomi (2009)	Level II *Fair*	1 RCT N=100	Adults undergoing off-pump CABG surgery	Hospital - planned surgery Iran	Tranexamic acid (IV) vs placebo	Transfusion incidence (pRBC/intraoperative)	0% vs 6%	*No difference* 0.24	*NA*
						Transfusion incidence (pRBC/0-4 hr)	0% vs 30%	*Favours tranexamic acid* <0.001	*NA*
						Transfusion incidence (pRBC/4-24 hr)	16.0% vs 18.0%	*No difference* 1.00	*NA*
						Transfusion incidence (FFP/0-4 hr)	4.0% vs 4.0%	*No difference* 1.00	*NA*
						Transfusion incidence (FFP/4-24 hr)	0% vs 0%	*No difference* NA	*NA*
						Transfusion incidence (RBC or FFP/up to 24 hr)	16.0% vs 54.0%	*Favours tranexamic acid* *<0.001*	*NA*
Orthopaedic surgery									
Henry (2007)	Level I *Good*	20 RCTs N=953	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.44 (0.33, 0.60)	*Favours tranexamic acid* <0.001	*Substantial* P*het*<0.001 (I^2=65%)
Kagoma (2009)	Level I *Good*	18 RCTs N=943	Adult patients undergoing hip and knee replacement surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Transfusion incidence	RR 0.47 (0.40, 0.55)	*Favours tranexamic acid* NR	*NR*
Alvarez (2008)	Level II *Fair*	1 RCT N=95	Adult patients undergoing total knee arthroplasty	Hospital – planned surgery Spain	Tranexamic acid (IV) vs placebo	Transfusion incidence (allogeneic and autologous blood)	2.2% vs 12.2%	*No difference* 0.11	*NA*
						Transfusion incidence (recovered blood)	4.3% vs 73.5%	*Favours tranexamic acid* <0.001	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
Elwatidy (2008)	Level II *Fair*	1 RCT N=64	Adults or children undergoing spine surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (IV) vs placebo	Transfusion incidence	12.5% vs 37.5%	*Favours tranexamic acid* 0.021	*NA*
Sadeghi (2007)	Level II *Good*	1 RCT N=67	Adults undergoing hip fracture surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Transfusion incidence (whole blood or pRBC)	37.5% vs 57.1%	*Favours tranexamic acid* 0.04	*NA*
						Transfusion incidence (FFP)	3.1% vs 0%	*No difference* >0.05	*NA*
						Transfusion incidence (platelets)	0% vs 0%	*No difference* NA	*NA*
						Transfusion incidence (any blood products)	37.5% vs 57.1%	*Favours tranexamic acid* 0.04	*NA*
Wong (2008)	Level II *Good*	1 RCT N=147	Adults undergoing spinal fusion surgery	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Transfusion incidence (pRBC/perioperative)	31% vs 40%	*No difference* 0.25	*NA*
						Transfusion incidence (AWB/perioperative)	32% vs 36%	*No difference* 0.65	*NA*
						Transfusion incidence (cell saver/perioperative)	45% vs 63%	*Favours tranexamic acid* 0.026	*NA*
						Transfusion incidence (FFP/perioperative)	7% vs 12%	*No difference* 0.27	*NA*
						Transfusion incidence (platelets/perioperative)	3% vs 3%	*No difference* 0.99	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
Wong (2008)	Level II *Good*	1 RCT N=147	Adults undergoing spinal fusion surgery	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Transfusion incidence (pRBC/intraoperative)	19% vs 23%	*No difference* 0.57	*NA*
						Transfusion incidence (AWB/intraoperative)	25% vs 28%	*No difference* 0.61	*NA*
						Transfusion incidence (cell saver/intraoperative)	45% vs 62%	*Favours tranexamic acid* 0.039	*NA*
						Transfusion incidence (FFP/intraoperative)	5% vs 9%	*No difference* 0.36	*NA*
						Transfusion incidence (platelets/intraoperative)	3% vs 3%	*No difference* 0.99	*NA*
Wong (2008)	Level II *Good*	1 RCT N=147	Adults undergoing spinal fusion surgery	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Transfusion incidence (pRBC/postoperative)	15% vs 28%	*No difference* 0.051	*NA*
						Transfusion incidence (AWB/postoperative)	13% vs 13%	*No difference* 0.97	*NA*
						Transfusion incidence (cell saver/postoperative)	3% vs 4%	*No difference* 0.66	*NA*
						Transfusion incidence (FFP/postoperative)	0% vs 0%	No difference NA	*NA*
						Transfusion incidence (platelets/postoperative)	0% vs 0%	No difference NA	*NA*
Liver surgery									
Henry (2007)	Level I *Good*	2 RCTs N=296	Adult patients undergoing liver surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.16 (0.00, 32.47)	*No difference* 0.50	*Substantial* P*het*<0.001 (I^2=93%)
Other surgery									
Henry (2007)	Level I/II Good/Fair	1 RCT N=59	Adult patients undergoing vascular surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.56 (0.33, 0.96)	*Favours tranexamic acid* *0.035*	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
Kongnyuy (2009)	Level I/II *Good/Good*	1 RCT N=100	Adult patients undergoing myomectomy	Hospital – planned surgery Turkey	Tranexamic acid (IV) vs placebo	Transfusion incidence	RR 1.71 (0.68, 4.30)	*No difference* 0.25	*NA*
Choi (2009)	Level II *Fair*	1 RCT N=61	Adult patients undergoing orthognathic surgery	Hospital – planned surgery China (Hong Kong)	Tranexamic acid (IV) vs placebo	Transfusion incidence	12.5% vs 24.1%	*No difference* 0.32	*NA*
PAEDIATRIC POPULATION/IV APROTININ									
Orthopaedic surgery									
Tzortzopoulou (2008)	Level II *Good*	2 RCT N=84	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Transfusion incidence	RR 0.84 (0.56, 1.27)	*No difference* 0.41	*None* P*het*=0.94 (I^2=0%)
ADULT POPULATION/TOPICAL TRANEXAMIC ACID									
Cardiac surgery									
Abrishami (2009)	Level I *Good*	2 RCTs N=233	Adult patients undergoing on-pump cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (topical) vs placebo	Transfusion incidence (allogeneic RBC)	RR 0.98 (0.75, 1.27)	*No difference* 0.88	*None* P*het*=0.69 (I^2=0%)
ADULT POPULATION/ORAL TRANEXAMIC ACID									
Cardiac surgery									
Gurusamy (2009)	Level I/II *Poor*	1 RCT N=214	Adults patients undergoing liver resection	Hospital – planned surgery China	Tranexamic acid (oral) vs no tranexamic acid	Transfusion incidence (allogeneic blood)	RR 0.03 (0.00, 0.46)	*Favours tranexamic acid* 0.012	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] Cochrane ratings defined as follows: Grade A, adequate allocation concealment; Grade B, uncertain allocation concealment; Grade C, inadequate allocation concealment.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on transfusion volume?		Evidence table ref[a]: POQ3.I8b.P2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I (Henry 2007/good quality) study which includes data from 11 RCTs and four additional level II studies (Taghaddomi 2009/fair quality; Alvarez 2008/fair quality; Elwatidy 2008/fair quality; Wong 2008/good quality) which provide data on the transfusion volume in patients who received transfusion. There was one pivotal Level I (Henry 2007/good quality) study which includes data from 14 RCTs and five additional Level II studies (Later 2009/good quality; Maddali 2007/good quality; Mehr-Aein 2007/good quality; Elwatidy 2008/fair quality; Sadeghi 2007/good quality) which provide data on transfusion volume in all patients (transfused or not).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results somewhat inconsistent between pivotal meta-analysis and additional RCTs. Consistency of individual studies within meta-analysis described below. Results either favour tranexamic acid or show no difference. Potential causes for differences between studies include different denominators used (all patients or transfused patients), different surgery types and different blood products transfused. Pivotal evidence – Henry 2007 Substantial heterogeneity (see note) in main analyses.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (units; all patients) – WMD -1.12 (-1.59, -0.64); 14 RCTs (N=965) Any surgery (units; transfused patients – WMD -0.51 (-1.06, 0.04); 11 RCTs (N=429) Supportive evidence – see Summary Table POQ3.18b.P2	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis. There were also analyses of patients undergoing cardiac surgery who had received ASA within 7 days prior to surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal reviews included studies from a wide range of countries. Included RCTs were from a number of different countries including several from the Middle East and Asia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I (good quality) study and four additional level II studies which provide data on the transfusion volume in patients who received transfusion. There was one pivotal Level I (good quality) study and five additional Level II studies which provide data on transfusion volume in all patients (transfused or not).
2. Consistency	B	Some inconsistency, likely due to different denominators (all vs transfused patients), surgery type and blood products.
3. Clinical impact	C	There was generally a slight to moderate reduction in transfusion volume associated with tranexamic acid therapy compared with no therapy
4. Generalisability	C	The results are generalisable to an adult surgical population; the majority of evidence is in cardiac and orthopaedic surgery.
5. Applicability	B	There were a reasonable number of studies conducted in different countries. The additional RCTs were conducted in the Netherlands, Oman, Iran, Saudi Arabia, Spain and Canada. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy may reduce the volume of allogeneic blood transfusion compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: ASA, acetylsalicylic acid; RCT, randomised controlled trial; SR, systematic review; WMD, weighted mean difference.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8b.P2 Characteristics and results of studies examining the effect of tranexamic acid on transfusion volume

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	14 RCTs N=965	Adult patients undergoing any surgery (all patients)	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Transfusion volume (units; allogeneic blood)	WMD -1.12 (-1.59, -0.64)	*Favours tranexamic acid* <0.001	*Substantial* P*het*<0.001 (I^2=73%)
	Level I *Good*	11 RCTs N=429	Adult patients undergoing any surgery (transfused patients only)	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Transfusion volume (units; allogeneic blood)	WMD -0.51 (-1.06, 0.04)	*No difference* 0.071	*Substantial* P*het*<0.001 (I^2=74%)
Cardiac surgery									
Later (2009)	Level II *Good*	1 RCT N=202	Adult patients undergoing first-time, non-complex cardiac surgery with CPB (all patients)	Hospital – planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Transfusion volume (units; pRBC)	Comparison of medians: 1.0 vs 2.0	*Favours tranexamic acid* 0.038	*NA*
Maddali (2007)	Level II Good	1 RCT N=222	Adults undergoing primary CABG surgery (all patients)	Hospital – planned surgery Oman	Tranexamic acid (IV) vs placebo	Transfusion volume (mL; total pRBC)	609 vs 952	*Favours tranexamic acid* 0.001	*NA*
						Transfusion volume (units; total FFP)	0.72 vs 1.6	*Favours tranexamic acid* <0.01	*NA*
						Transfusion volume (units; total platelets)	0.7 vs 0.8	*No difference* NS	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adults undergoing primary off-pump CABG surgery (all patients)	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Transfusion volume (units; whole blood or pRBC)	0.46 vs 0.94	*Favours tranexamic acid* 0.001	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Taghaddomi (2009)	Level II *Fair*	1 RCT N=100	Adult patients undergoing off-pump CABG surgery (transfused patients only)	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Transfusion volume (units; pRBC/intraoperative)	0 vs 1	*No difference* 0.36	*NA*
						Transfusion volume (units; pRBC/0-4 postoperative)	0 vs 1.3	*Favours tranexamic acid* <0.001	*NA*
						Transfusion volume (units; pRBC/4-24 postoperative)	1 vs 1	*No difference* 0.5	*NA*
						Transfusion volume (units; FFP/0-4 postoperative)	3 vs 2.5	*No difference* 0.8	*NA*
						Transfusion volume (units; FFP/4-24 postoperative)	0 vs 0	*No difference* NA	*NA*
						Transfusion volume (units; FFP/4-24 postoperative)	1 vs 1.1	*No difference* NR	*NA*
Orthopaedic surgery									
Alvarez (2008)	Level II *Fair*	1 RCT N=95	Adult patients undergoing total knee arthroplasty (transfused patients only)	Hospital – planned surgery Spain	Tranexamic acid (IV) vs placebo	Transfusion volume (total RBC; units)	1 vs 1.8	NR	*NA*
						Transfusion volume (allogeneic RBC; units)	1 vs NR (8 units in unspecified number of patients)	NR	*NA*
						Transfusion volume (autologous RBC; units)	0 vs NR (3 units in unspecified number of patients)	NR	*NA*
Elwatidy (2008)	Level II *Fair*	1 RCT N=64	Adult or paediatric patients undergoing spine surgery (all patients)	Hospital – planned surgery Saudi Arabia	Tranexamic acid (IV) vs placebo	Transfusion volume (mL)	94 vs 531	*Favours tranexamic acid* 0.008	*NA*
			Adult or paediatric patients undergoing spine surgery (transfused patients only)			Transfusion volume (units)	1.5 vs 2.8[d]	*NA*	*NA*
Sadeghi (2007)	Level II *Good*	1 RCT N=67	Adult patients undergoing hip fracture surgery (all patients)	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Transfusion volume (whole blood or pRBC; units)	1.25 vs 1.95	*Favours tranexamic acid* 0.001	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Wong (2008)	Level II *Good*	1 RCT N=147	Adult patients undergoing spinal fusion surgery (transfused patients)[e]	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Transfusion volume (mL; pRBC/perioperative)	266 vs 406	*No difference* 0.16	*NA*
						Transfusion volume (mL; AWB/perioperative)	222 vs 315	*No difference* 0.30	*NA*
						Transfusion volume (mL; cell-saver/perioperative)	218 vs 334	*No difference* 0.083	*NA*
						Transfusion volume (mL; pRBC/intraoperative)	169 vs 208	*No difference* 0.61	*NA*
						Transfusion volume (mL; AWB/intraoperative)	150 vs 249	*No difference* 0.24	*NA*
						Transfusion volume (mL; cell-saver/intraoperative)	210 vs 323	*No difference* 0.086	*NA*
						Transfusion volume (mL; pRBC/postoperative)	97 vs 198	*No difference* 0.057	*NA*
						Transfusion volume (mL; AWB/postoperative)	72 vs 66	*No difference* 0.85	*NA*
						Transfusion volume (mL; cell-saver/postoperative)	8 vs 11	*No difference 0.73*	*NA*
PAEDIATRIC POPULATION/IV TRANEXAMIC ACID									
Cardiac surgery									
Schouten (2009)	Level I *Good*	NR N=460	Paediatric patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Transfusion volume (mL/kg; pRBC)	WMD -7 (-10, -5)	*Favours tranexamic acid* NR	*None* P*het*=NR (I^2=6%)
		NR N=419	Paediatric patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Transfusion volume (mL/kg; plasma)	WMD -7 (-9, -4)	*Favours tranexamic acid NR*	*None* P*het*=NR (I^2=0%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
		NR N=370	Paediatric patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Transfusion volume (mL/kg; thrombo)	WMD -5 (-7, -3)	*Favours tranexamic acid NR*	*None* Phet=NR (I^2=0%)
Orthopaedic surgery									
Schouten (2009)	Level I *Good*	2 RCTs N=84	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Transfusion volume (mL; pRBC)	WMD -349 (-620, -77)	*Favours tranexamic acid* NR	*None* Phet=NR (I^2=0%)
						Transfusion volume (mL; plasma)	WMD -15 (-127, -98)	*Favours tranexamic acid NR*	*None* Phet=NR (I^2=24%)
Tzortzopoulou (2008)	Level I *Good*	2 RCT N=84	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Transfusion volume (mL)	WMD -395 (-688, -103)	*Favours ε-aminocaproic acid* 0.0081	*None* Phet=0.51 (I^2=0%)
ADULT POPULATION/TOPICAL APROTININ									
Abrishami (2009)	Level I	3 RCTs N=229	Adult patients undergoing on-pump cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (topical) vs no tranexamic acid	Transfusion volume (units)	WMD -1.58 (-2.26, -0.90)	*Favours tranexamic acid* <0.001	*None* Phet=0.29 (I^2=20%)
Fawzy (2009)	Level II Good	1 RCT N=38	Adult patients undergoing primary elective CABG surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (topical) vs placebo	Transfusion volume (units; pRBC/postoperative)	Comparison of medians: 1.0 vs 1.0	*No difference 0.82*	*NA*
						Transfusion volume (units; FFP/postoperative)	Comparison of medians: 0 vs 2.0	*No difference 0.42*	*NA*
						Transfusion volume (units; plasma/postoperative)	Comparison of medians: 0 vs 2.0	*Favours tranexamic acid 0.03*	*NA*

Note: Studies/analyses providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies/analyses provide supportive evidence.
Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; *het*, heterogeneity; IV, intravenous; kg, kilogram; mL, millilitre; NA, not applicable; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; SMD, standardised mean difference; WMD, weighted mean difference.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between aprotinin and no aprotinin.
[d] One patient received 14 units of blood. If this person is excluded the mean number of units transfused per transfused patient is 1.8.
[e] Not specifically stated but appears to be based on transfused patients only.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on blood loss?		Evidence table ref[a]: POQ3.I8b.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from up to 23 RCTs, two supportive level I studies (Brown 2007/fair quality; Kagoma 2009/good quality), two supportive Level I/II studies which included data from one RCT each (McIlroy 2009/good-fair quality; Kongnyuy 2009/good-good quality) and 13 additional RCTs published since the pivotal review (Jimenez 2007/good quality; Later 2009/good quality; Maddali 2007/good quality; Mehr-Aein 2007/good quality; Taghaddomi 2009/fair quality; Alvarez 2008/fair quality; Elwatidy 2008/good quality; Sadeghi 2007/good quality; Wong 2008/good quality; Chen 2008/fair quality; Choi 2009/fair quality; Mayur 2007/poor quality; Sekhavat 2009/poor quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 Substantial significant heterogeneity (see note) in main analyses (postoperative) and subgroup analyses. Differences likely due to different surgeries and measurement and timing of blood loss. Supportive evidence Most results showed significantly less blood loss with tranexamic acid compared with no tranexamic acid.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (mL; total blood loss) – WMD -444 (-572, -315); 17 RCTs (N=955) Cardiac surgery (mL; total blood loss) – WMD -440 (-607, -273); 3 RCTs (N=245) Orthopaedic surgery (mL; total blood loss) – WMD -440 (-591, -288); 14 RCTs (N=690) Supportive evidence – See Summary Table POQ3.I8b.P3	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis. There were also analyses of patients undergoing cardiac surgery who had received ASA within 7 days prior to surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal reviews included studies from a wide range of countries. Included RCTs were from a number of different countries including several from the Middle East and Asia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), two supportive level I studies, two supportive Level I/II study and 13 additional RCTs.
2. Consistency	B	Some inconsistency, likely due to different surgery types and timing of outcome measurement. Inconsistency related to magnitude of effect rather than direction of effect.
3. Clinical impact	B	There was generally a substantial reduction in blood loss associated with TXA.
4. Generalisability	C	The results are generalisable to a general surgical population.
5. Applicability	B	Overall there were a reasonable number of studies conducted in a range of countries. Individual additional RCTs were conducted in Spain, The Netherlands, Oman, Iran, Saudi Arabia, Canada, Turkey, Hong Kong and India. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy reduces blood loss compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: ASA, acetylsalicylic acid; RCT, randomised controlled trial; SR, systematic review; TXA, tranexamic acid; WMD, weighted mean difference.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8b.P3 Characteristics and results of studies examining the effect of tranexamic acid on blood loss

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	10 RCTs N=553	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Intraoperative blood loss (mL)	WMD -55 (-105, -4.5)	*Favours tranexamic acid* 0.033	*None* *Phet*=0.26 (I^2=20%)
		23 RCTs N=1423	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Postoperative blood loss (mL)	WMD -248 (-313, -183)	*Favours tranexamic acid* <0.001	*Substantial* *Phet*<0.001 (I^2=76%)
		18 RCTs N=955	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Total blood loss (mL)	WMD -444 (-572, -315)	*Favours tranexamic acid* <0.001	*Substantial* *Phet*<0.001 (I^2=72%)
Cardiac surgery									
Henry (2007)	Level I *Good*	3 RCTs N=144	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Intraoperative blood loss (mL)	WMD -287 (-482, -93)	*Favours tranexamic acid* 0.0038	*None* *Phet*=0.66 (I^2=0%)
		17 RCTs N=1130	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Postoperative blood loss (mL)	WMD -263 (-319, -207)	*Favours tranexamic acid* <0.001	*Moderate* *Phet*=0.01 (I^2=48%)
		9 RCTs N=302	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Postoperative blood loss (mL; total dose < 2.0 g)	WMD -252 (-352, -151)	*Favours tranexamic acid* <0.001	*Moderate* *Phet*=0.07 (I^2=45%)
		8 RCTs N=828	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Postoperative blood loss (mL; total dose 2.0-10.0 g)	WMD -272 (-341, -205)	*Favours tranexamic acid* <0.001	*Substantial* *Phet*=0.03 (I^2=54%)
		3 RCTs N=245	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Total blood loss (mL)	WMD -440 (-607, -273)	*Favours tranexamic acid* <0.001	*None* *Phet*=0.82 (I^2=0%)
Brown (2007)	Level I Fair	11 RCTs N=1100	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Total blood loss (mL)	WMD -285 (-394, -175)	*Favours tranexamic acid* <0.001	*NR*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity[b]*
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
McIlroy(2009)	Level I/II *Good/Fair*	1 RCT N=79	Adult patients receiving ASA undergoing cardiac surgery	Hospital – planned surgery Unknown	Lysine analogues (IV) vs placebo	Postoperative chest tube blood loss (mL)	WMD -189 (-287, -91)	*Favours lysine analogues* <0.001	*Substantial* P*het*=0.05 I2=67%
Jimenez (2007)	Level II *Good*	1 RCT N=50	Adults undergoing cardiopulmonary bypass surgery	Hospital - planned surgery Spain	Tranexamic acid (IV) vs placebo	24-hour blood loss (mL)	464 vs 1037	*Favours tranexamic acid* <0.01	*NA*
						Total blood loss (mL)	835 vs 1466	*Favours tranexamic acid* <0.01	*NA*
Later (2009)	Level II *Good*	1 RCT N=202	Adults undergoing first-time, non-complex cardiac surgery with CPB	Hospital - planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Total mediastinal chest tube blood loss (mL)	760 vs 860	*Favours tranexamic acid* 0.034	*NA*
Maddali (2007)	Level II *Good*	1 RCT N=222	Adults undergoing primary CABG surgery	Hospital – planned surgery Oman	Tranexamic acid (IV) vs placebo	Total drainage (mL)	633 vs 981	*Favours tranexamic acid* 0.001	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adults undergoing off-pump CABG surgery	Hospital - planned surgery Iran	Tranexamic acid (IV) vs placebo	Postoperative blood loss 0-2 hr (mL)	90 vs 180	*Favours tranexamic acid* <0.001	*NA*
						Postoperative blood loss 2-6 hr (mL)	190 vs 290	*Favours tranexamic acid* 0.001	*NA*
						Total postoperative blood loss (mL)	320 vs 480	*Favours tranexamic acid* 0.001	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Taghaddomi (2009)	Level II *Fair*	1 RCT N=100	Adults undergoing off-pump CABG surgery	Hospital - planned surgery Iran	Tranexamic acid (IV) vs placebo	Intraoperative bleeding (mL)	467 vs 531	*No difference* 0.62	*NA*
						Postoperative bleeding (mL; 0-4 hr)	87 vs 210	*Favours tranexamic acid* 0.005	*NA*
						Postoperative bleeding (mL; 4-24 hr)	462 vs 570	*No difference* 0.07	*NA*
						Total bleeding (mL; within 24 hr)	471 vs 844	*Favours tranexamic acid* <0.001	*NA*
Orthopaedic surgery									
Henry (2007)	Level I *Good*	7 RCTs N=409	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Intraoperative blood loss (mL)	WMD -30 (-69, 10)	*No difference* 0.14	*None* P*het*=0.69 (I^2=0%)
		6 RCTs N=293	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Postoperative blood loss (mL)	WMD -210 (-384, -35)	*Favours tranexamic acid* 0.019	*Substantial* P*het*<0.001 (I^2=91%)
		14 RCT N=690	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Total blood loss (mL)	WMD -440 (-591, -288)	*Favours tranexamic acid* <0.001	*Substantial* P*het*<0.001 (I^2=78%)
Kagoma (2009)	Level I *Good*	15 RCTs N=778	Adults undergoing total knee or hip replacement	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Total bleeding[d] (mL)	WMD -393 (-442, -345)	*Favours tranexamic acid* NR	*NR*
Alvarez (2008)	Level II *Fair*	1 RCT N=95	Adult patients undergoing total knee arthroplasty	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Chest-tube blood loss (mL; 0-6 hr postoperative)	159 vs 534	*Favours tranexamic acid* <0.001	*NA*
						Chest-tube blood loss (mL; 6 hr – 4 day postoperative)	132 vs 132	*No difference* 0.98	*NA*
						Total chest-tube blood loss (mL)	170 vs 551	*Favours tranexamic acid* <0.001	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Elwatidy (2008)	Level II *Fair*	1 RCT N=64	Adult and paediatric patients undergoing spine surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (IV) vs placebo	Intraoperative blood loss (mL)	311 vs 585	*Favours tranexamic acid* 0.03	*NA*
						Wound drain blood loss (mL)	98 vs 215	*Favours tranexamic acid* 0.004	*NA*
						Total blood loss (mL)	406 vs 800	*Favours tranexamic acid* 0.007	*NA*
Sadeghi (2007)	Level II *Good*	1 RCT N=67	Adults undergoing hip fracture surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Perioperative blood loss (mL)	652 vs 1108	*Favours tranexamic acid* 0.003	*NA*
						Postoperative blood loss 1 hr (mL)	111 vs 139	*No difference* 0.39	*NA*
						Postoperative blood loss 2 hr (mL)	192 vs 246	*No difference* 0.28	*NA*
						Postoperative blood loss 5 hr (mL)	255 vs 323	*No difference* 0.31	*NA*
						Postoperative blood loss 12 hr (mL)	296 vs 375	*No difference* 0.20	*NA*
						Postoperative blood loss 24 hr (mL)	300 vs 390	*No difference* 0.11	*NA*
						Total blood loss (mL)	960 vs 1484	*Favours tranexamic acid* 0.001	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Wong (2008)	Level II *Good*	1 RCT N=147	Adults undergoing spinal fusion surgery	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Perioperative blood loss (estimated; mL)	1592 vs 2138	*Favours tranexamic acid* 0.026	*NA*
						Perioperative blood loss (calculated; mL)	3079 vs 4363	*Favours tranexamic acid* 0.017	*NA*
						Perioperative RBC loss (calculated; mL)	1078 vs 1527	*Favours tranexamic acid* 0.017	*NA*
						Intraoperative blood loss (estimated; mL)	1203 vs 1600	*Favours tranexamic acid* 0.044	*NA*
						Postoperative blood loss (estimated; mL)	536 vs 737	*Favours tranexamic acid* 0.039	*NA*
Liver surgery									
Henry (2007)	Level I/II *Good/Poor*	1 RCT N=20	Adult patients undergoing orthotopic liver transplant	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Blood loss (mL)	MD -6552 (-14330, 1226)	*No difference* 0.099	*NA*
Other surgery									
Kongnyuy (2009)	Level I/II *Good/Good*	1 RCT N=100	Adult patients undergoing myomectomy	Hospital – planned surgery Turkey	Tranexamic acid (IV) vs placebo	Transection blood loss (mL)	MD -243 (-460, -26)	*Favours tranexamic acid* 0.028	*NA*
Chen (2008)	Level II *Fair*	1 RCT N=55	Adult patients undergoing head and neck surgery	Hospital – planned surgery Taiwan	Tranexamic acid (IV) vs placebo	Perioperative bleeding (mL)	87 vs 116	*No difference* 0.392	*NA*
						Drainage amount (mL)	50 vs 89	*Favours tranexamic acid* 0.04	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity[b]*
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Choi (2009)	Level II *Fair*	1 RCT N=44	Adult patients undergoing anterior mandibular surgery	Hospital – planned surgery Hong Kong	Tranexamic acid (IV) vs placebo	Intraoperative or postoperative blood loss (mL)	277 vs 416	*No difference* NS	*NA*
		1 RCT N=61	Adult patients undergoing maxillary surgery	Hospital – planned surgery Hong Kong	Tranexamic acid (IV) vs placebo	Intraoperative or postoperative blood loss (mL)	428 vs 644	*Favours tranexamic acid* <0.05	*NA*
		1 RCT N=41	Adult patients undergoing ramus surgery	Hospital – planned surgery Hong Kong	Tranexamic acid (IV) vs placebo	Intraoperative or postoperative blood loss (mL)	287 vs 329	*No difference* NS	*NA*
		1 RCT N=61	Adult patients undergoing any orthognathic surgery	Hospital – planned surgery Hong Kong	Tranexamic acid (IV) vs placebo	Intraoperative or postoperative blood loss (mL)	879 vs 1257	*Favours tranexamic acid* <0.05	*NA*
Mayur (2007)	Level II *Poor*	1 RCT N=100	Adult patients undergoing caesarean section	Hospital – planned surgery India	Tranexamic acid (IV) vs placebo	Post-partum haemorrhage (placental delivery to end of surgery; mL)	299 vs 340	*No difference* 0.056	*NA*
						Post-partum haemorrhage (end of surgery to 2 hr post-partum; mL)	76 vs 133	*Favours tranexamic acid 0.001*	*NA*
						Post-partum haemorrhage (placental delivery to 2 hr post-partum; mL)	375 vs 473	*Favours tranexamic acid 0.003*	*NA*
Sekhavat (2009)	Level II *Poor*	1 RCT N=90	Adult patients undergoing caesarean section	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Blood loss up to 2 hr postoperative (mL)	28 vs 37	*Favours tranexamic acid <0.001*	*NA*
PAEDIATRIC POPULATION/IV TRANEXAMIC ACID									
Cardiac surgery									
Schouten (2009)	Level I *Good*	NR N=542	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Blood loss (mL/kg)	WMD -11 (-13, -8)	*Favours tranexamic acid* NR	*Moderate* P*het*=NR (I^2=31)

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Orthopaedic surgery									
Schouten (2009)	Level I *Good*	2 RCTs N=84	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Blood loss (mL)	WMD -682 (-1149, -214)	*Favours tranexamic acid* NR	*Unclear* *Phet*=NR (I^2=24)
Tzortzopoulou (2008)	Level I *Good*	2 RCTs N=84	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Blood loss (mL)	WMD -682 (-1149, -214)	*Favours tranexamic acid* 0.0042	*Mild* *Phet*=0.25 (I^2=24)
ADULT POPULATION/TOPICAL TRANEXAMIC ACID									
Cardiac surgery									
Abrishami (2009)	Level I *Good*	4 RCTs N=269	Adult patients undergoing on-pump cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (topical) vs placebo	24-hr postoperative chest-tube loss (mL)	WMD -250 (-465, -35)	*Favours tranexamic acid* 0.02	*Substantial* *Phet*<0.001 (I^2=95%)
Fawzy (2009)	Level II *Good*	1 RCT N=38	Adult patients undergoing primary isolated CABG surgery	Hospital – planned surgery Unknown	Tranexamic acid (topical) vs placebo	24-hr chest tube blood loss (mL)	626 vs 1040	*Favours tranexamic acid* 0.04	*NA*
						Total chest-tube blood loss (mL)	656 vs 1056	*Unclear* NR	*NA*
Jabalameli (2006)	Level II *Poor*	1 RCT N=56	Adult patients undergoing endoscopic sinus surgery	Hospital – planned surgery Iran	Tranexamic acid (topical) vs placebo	Intraoperative blood loss (mL)	174 vs 229	*Favours tranexamic acid* <0.05	*NA*
Other surgery									
Athanasiadis (2007)	Level II *Fair*	1 RCT N=30	Adult patients undergoing endoscopic sinus surgery	Hospital – planned surgery Australia	Tranexamic acid 100 mg (topical) vs placebo	Bleeding grading scales[e] at 0, 2, 4, 6, 8 and 10 mins	NR	*Favours tranexamic acid* <0.05	*NA*
					Tranexamic acid 1 g (topical) vs placebo	Bleeding grading scales[e] at 0, 2, 4, 6, 8 and 10 mins	NR	*Favours tranexamic acid* <0.05	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
ADULT POPULATION/ORAL TRANEXAMIC ACID									
Liver surgery									
Gurusamy (2009)	Level I/II *Fair*	1 RCT N=214	Adult patients undergoing liver surgery	Hospital – planned surgery China	Tranexamic acid (oral) vs placebo	Transection blood loss (mL)	MD -260 (-435, -85)	*Favours tranexamic acid* 0.0036	*NA*
						Operative blood loss (mL)	MD -300 (-502, -98)	*Favours tranexamic acid* 0.0036	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; mL, millilitres; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SMD, standardised mean difference; WMD, weighted mean difference.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between tranexamic acid and no tranexamic acid.
[d] Total bleeding measured intraoperatively by weighing surgical sponges, postoperatively through drainage or perioperatively through the haemoglobin balance method which measures loss through comparison of pre- and postoperative haemoglobin concentrations (haematoma volumes as well as hidden or internal blood loss were excluded).
[e] Wormald grading scale and Boezaart grading scale.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on mortality?		Evidence table ref[a]: POQ3.I8b.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from 16 RCTs, one supportive Level I study (Brown 2007/fair quality) and four additional RCTs published since the pivotal review (Jimenez 2007/good quality; Later 2009/good quality; Mehr-Aein 2007/good quality; Sadeghi 2007/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in main analyses Supportive evidence – all studies showed no difference between tranexamic acid and no tranexamic acid.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – 1.2% vs 2.4%; RR 0.60 (0.32, 1.12); 16 RCTs (N=1684) Cardiac surgery – 0.9% vs 1.9%; RR 0.55 (024, 1.25); 11 RCTs (N=1390) Supportive evidence – Brown 2007 (see also Summary table POQ3.I8b.P4) Cardiac surgery – no absolute risks reported; RR 0.67 (0.33, 1.37); 18 RCTs (N=2229)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although 11/16 RCTs in the pivotal review were in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal reviews included studies from a wide range of countries. Included RCTs were from a number of different countries including several from the Middle East and Asia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

Generalisability made a C as most studies were conducted in cardiac surgery but the evidence statement has been applied to the whole surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study and four additional RCTs.
2. Consistency	A	Results are consistent. There was no heterogeneity in the pivotal study.
3. Clinical impact	D	While there is no significant difference in mortality between intravenous tranexamic acid therapy and no therapy, and the risk estimates suggest no increased risk, the findings are uncertain due to underpowering.
4. Generalisability	C	The results are generalisable to a surgical population; however, most studies were conducted in cardiac surgery.
5. Applicability	B	There were a moderate number of studies conducted in a range of countries. The additional RCTs were conducted in Spain, The Netherlands and Iran. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on mortality compared with no therapy is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: RCT, randomised controlled trial; RR, risk ratio; SR, systematic review.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8b.P4 Characteristics and results of studies examining the effect of tranexamic acid on mortality

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	16 RCTs N=1684	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Mortality	RR 0.60 (0.32, 1.12)	*No difference* 0.11	*None* P*het*=0.84 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	11 RCTs N=1390	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Mortality	RR 0.55 (0.24, 1.25)	*No difference* 0.15	*None* P*het*=0.73 (I^2=0%)
Henry (2009)	Level I *Good*	11 RCTs N=1390	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Mortality	RR 0.55 (0.24, 1.25)	*No difference* NR	*NR*
Brown (2007)	Level I *Fair*	18 RCTs N=2229	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Mortality	RR 0.67 (0.33, 1.37)	*No difference* 0.276	*NR*
Jimenez (2007)	Level II *Good*	1 RCT N=50	Adult patients undergoing cardiopulmonary bypass surgery	Hospital – planned surgery Spain	Tranexamic acid (IV) vs placebo	In-hospital mortality	0% vs 0%	*No difference* NA	*NA*
Later (2009)	Level II *Good*	1 RCT N=202	Adult patients undergoing first-time, non-complex cardiac surgery with CPB	Hospital – planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	In-hospital mortality	1% vs 1%	*No difference* 1.00	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adult patients undergoing primary CABG surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	In-hospital mortality	0% vs 0%	*No difference* NA	*NA*
Orthopaedic surgery									
Sadeghi (2007)	Level II *Good*	1 RCT N=67	Adult patients undergoing hip fracture surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	In-hospital mortality	0% vs 3%	*No difference* 1.00	*NA*
ADULT POPULATION/TOPICAL TRANEXAMIC ACID									
Cardiac surgery									
Fawzy (2009)	Level II Good	1 RCT N=28	Adult patients undergoing primary isolated CABG surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (topical) vs placebo	In-hospital mortality	0% vs 0%	*No difference NA*	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/ORAL TRANEXAMIC ACID									
Cardiac surgery									
Gurusamy (2009)	Level I/II *Poor*	1 RCT N=214	Adults patients undergoing liver resection	Hospital – planned surgery China	Tranexamic acid (oral) vs no tranexamic acid	Mortality	0% vs 0%	*No difference* NA	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between tranexamic acid and no tranexamic acid.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on morbidity (myocardial infarction)?		Evidence table ref[a]: POQ3.I8b.P5 (MI)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality), one supportive Level I study (Brown 2007/fair quality) and four additional RCTs (Later 2009/good quality; Mehr-Aein 2007/good quality; Taghaddomi 2009/fair quality; Wong 2008/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in main analyses Supportive evidence – nearly all studies showed no difference between tranexamic acid and no tranexamic acid.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – 1.7% vs 1.9%; RR 0.96 (0.48, 1.90); 12 RCTs (N=1344) Cardiac surgery – 1.5% vs 1.9%; RR 0.91 (0.44, 1.88); 9 RCTs (N=1048) Supportive evidence – Brown 2007 (see also Summary Table POQ3.I8b.P5 (MI) Cardiac surgery – no absolute risks reported; RR 0.94 (0.51, 1.74) (N=2219)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis of the pivotal review but 9/12 included RCTs in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review included studies from a wide range of countries. Included RCTs were from a number of different countries including The Netherlands, Iran and Canada.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

CRG concerned regarding the definition of MI in the individual included studies.

Generalisability made a C as most studies were conducted in cardiac surgery but the evidence statement is being applied to the whole surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study and four additional RCTs.
2. Consistency	A	There was no heterogeneity in the pivotal level I evidence. Additional studies were consistent.
3. Clinical impact	D	There was no significant difference in the risk of myocardial infarction between intravenous tranexamic acid therapy and no therapy.
4. Generalisability	C	The results are generalisable to a surgical population; however, most studies were conducted in cardiac surgery.
5. Applicability	B	A reasonable number of studies were conducted in a range of countries. The additional RCTs were conducted in The Netherlands, Iran and Canada. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy does not appear to have an effect on risk of myocardial infarction compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SR, systematic review.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8b.P5 (MI) Characteristics and results of studies examining the effect of tranexamic acid on morbidity (myocardial infarction)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	12 RCTs N=1344	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Myocardial infarction	RR 0.96 (0.48, 1.90)	*No difference* 0.91	*None* P*het*=0.96 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	9 RCTs N=1048	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Myocardial infarction	RR 0.91 (0.44, 1.88)	*No difference* 0.79	*None* P*het*=0.91 (I^2=0%)
Henry (2009)	Level I *Good*	10 RCTs N=1148	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs placebo	Myocardial infarction	RR 0.86 (0.43, 1.75)	*No difference* NR	*NR*
Brown (2007)	Level I *Fair*	16 RCTs N=2219	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Tranexamic acid (IV) vs placebo	Myocardial infarction	RR 0.94 (0.51, 1.74)	*No difference* 0.85	*NR*
Later (2009)	Level II *Good*	1 RCT N=202	Adult patients undergoing first-time, non-complex cardiac surgery with CPB	Hospital – planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Perioperative myocardial infarction	0% vs 8%	*Favours tranexamic acid* 0.007	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adult patients undergoing primary CABG surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Myocardial infarction	0% vs 0%	*No difference* NA	*NA*
Taghaddomi (2009)	Level II *Fair*	1 RCT N=100	Adult patients off-pump CABG surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Myocardial infarction	0% vs 0%	*No difference* NA	*NA*
						Myocardial ischaemia	0% vs 0%	*No difference* NA	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
Orthopaedic surgery									
Wong (2008)	Level II *Good*	1 RCT N=147	Adult patients undergoing spinal fusion surgery	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Myocardial infarction	1% (asymptomatic only) vs 0%	*No difference* NA	*NA*
ADULT POPULATION/TOPICAL TRANEXAMIC ACID									
Cardiac surgery									
Fawzy (2009)	Level II Good	1 RCT N=38	Adult patients undergoing primary isolated CABG surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (topical) vs placebo	In-hospital myocardial infarction	0% vs 0%	*No difference* *NA*	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between tranexamic acid and no tranexamic acid.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on morbidity (renal)?		Evidence table ref[a]: POQ3.I8b.P5 (renal)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from 4 RCTs, one supportive Level I study (Brown 2007/fair quality) and two additional RCTs published since the pivotal review (Later 2009/good quality; Mehr-Aein 2007/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results inconsistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in analysis. Supportive evidence While all results not statistically significant, point estimates from Brown meta-analyses for renal failure and renal dysfunction were in the opposite direction to Henry 2007 point estimate for both outcomes combined. 2 included RCTs were consistent with Henry result.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Cardiac surgery (renal failure/dysfunction) – 0.9% vs 1.4%; RR 0.73 (0.16, 3.32); 4 RCTs (N=400) Supportive evidence – Brown 2007 Cardiac surgery (renal failure) – no absolute risks reported; RR 1.43 (0.30, 6.85); 3 RCTs (N=840) Cardiac surgery (renal dysfunction) - no absolute risks reported; RR 2.02 (0.73, 5.60); 4 RCTs (N=684) See also Summary Table POQ3.I8b.P5 (renal)	A	Very large
	B	Substantial
	C	Moderate
	D	Inconsistent
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review included studies from a number of countries. Included RCTs were from The Netherlands and Iran.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

Brown defined renal outcomes as follows: (i) renal failure defined as a new onset of dialysis except in one study where it was defined as a ≥ 2 mg/dL creatinine level; (ii) renal dysfunction defined as a ≥ 0.5 mg/dL increase in creatinine.

Later 2009 RCT defined outcomes as follows: (i) renal failure as defined by Mangano (2006): required a postoperative serum creatinine of at least 2.0 mg/dL with an increase over the preoperative baseline level of at least 0.7 mg/dL; (ii) renal complication as defined by the RIFLE classification: risk of renal dysfunction defined as a 1.5 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 6 hours. Kidney injury was defined as a 2 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 12 hours, whilst renal failure was defined as a 3 times increase in perioperative creatinine plasma concentration or a urine output < 0.3 mL/kg/h in 24 hours.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study and two additional RCTs.
2. Consistency	D	Different direction of point estimate for pivotal and supportive Level I studies.
3. Clinical impact	D	There was no difference in risk of renal failure/dysfunction in the primary study but there was potentially an increased risk in the supportive study; thus the results are not consistent.
4. Generalisability	B	The results are generalisable to a cardiac surgical population.
5. Applicability	B	A small number of studies were conducted in a range of countries. The additional RCTs were conducted in The Netherlands and Iran. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of intravenous tranexamic acid therapy on risk of renal failure or dysfunction, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: RCT, randomised controlled trial; RR, risk ratio; SR, systematic review,
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.P5 (renal) Characteristics and results of studies examining the effect of tranexamic acid on morbidity (renal failure/dysfunction)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Cardiac surgery									
Henry (2007)	Level I *Good*	4 RCTs N=400	Adult patients undergoing any surgery	Hospital – planned surgery Unknown[c]	Tranexamic acid (IV) vs no tranexamic acid	Renal failure/dysfunction	RR 0.73 (0.16, 3.32)	*No difference* 0.68	None P*het*=0.69 (I^2=0%)
Brown (2007)	Level I *Fair*	3 RCTs N=840	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Renal failure[d]	RR 1.43 (0.30, 6.85)	*No difference* 0.66	NR
		4 RCTs N=684	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Renal dysfunction[e]	RR 2.02 (0.73, 5.60)	*No difference* 0.18	NR
Later (2009)	Level II *Good*	1 RCT N=202	Adult patients undergoing first-time, non-complex cardiac surgery with CPB	Hospital – planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Renal failure[f]	3% vs 3%	*No difference* 1.00	*NA*
						Renal complication[g]	8% vs 18%	*No difference* 0.059	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adult patients undergoing primary CABG	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Renal dysfunction (creatinine > 2 mg/dL)	0% vs 3%	*No difference* >0.05	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NA, not applicable; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between tranexamic acid and no tranexamic acid.
[d] Renal failure defined as a new onset of dialysis except in one study where it was defined as a ≥ 2 mg/dL creatinine level.
[e] Renal dysfunction defined as a ≥ 0.5 mg/dL increase in creatinine.
[f] Renal failure as defined by Mangano (2006)[3]. Required a postoperative serum creatinine of at least 2.0 mg/dL with an increase over the preoperative baseline level of at least 0.7 mg/dL.
[g] Renal complication as defined by the RIFLE classification[4]. Risk of renal dysfunction defined as a 1.5 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 6 hours. Kidney injury was defined as a 2 times increase in perioperative creatinine plasma concentration or a urine output < 0.5 mL/kg/h in 12 hours, whilst renal failure was defined as a 3 times increase in perioperative creatinine plasma concentration or a urine output < 0.3 mL/kg/h in 24 hours.

[3] Mangano et al (2006) The risk associated with aprotinin in cardiac surgery. NEJM 354:353-365.
[4] Kuitunen et al (2006) Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. Ann Thorac Surg 81: 542-546.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on morbidity (stroke)?		Evidence table ref[a]: POQ3.I8b.P5 (stroke)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from 7 RCTs, one supportive Level I study (Brown 2007/fair quality) and one additional RCT (Later 2009/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in main analyses. Supportive evidence Similar results between systematic reviews and single additional RCT.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – 1.4% vs 1.1%; RR 1.25 (0.47, 3.31); 7 RCTs (N=937) Cardiac surgery – 1.3% vs 0.8%; RR 1.52 (0.52, 4.41); 5 RCTs (N=841) Supportive evidence – Brown 2007 (see also Summary Table POQ3.I8b.P5 (stroke) Cardiac surgery – no absolute risks reported; RR 1.31 (0.59, 2.93); 15 RCTs (N=2098)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. Most evidence in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review included studies from a number of countries. The additional included RCT was from The Netherlands.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

Generalisability made a C as most studies in cardiac surgery but evidence statement being applied to the whole surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study and one additional RCT.
2. Consistency	A	There was no heterogeneity in the pivotal study. The supportive study was consistent. The additional RCT was underpowered to detect a difference in stroke between tranexamic acid therapy and no therapy.
3. Clinical impact	D	Results show a slightly increased risk with no significant difference (9/711 versus 5/634 in cardiac surgery) but studies likely underpowered to detect a difference in stroke.
4. Generalisability	C	The results are generalisable to a surgical population; however, most studies conducted in cardiac surgery.
5. Applicability	B	Studies were conducted in a range of countries. The additional RCT was conducted in The Netherlands. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on risk of stroke, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: RCT, randomised controlled trial; RR, risk ratio; SR, systematic review.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8b.P5(stroke) Characteristics and results of studies examining the effect of tranexamic acid on morbidity (stroke)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	7 RCTs N=937	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Stroke	RR 1.25 (0.47, 3.31)	*No difference* 0.65	*None* P*het*=0.79 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	5 RCTs N=841	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Stroke	RR 1.52 (0.52, 4.41)	*No difference* 0.44	*None* P*het*=0.78 (I^2=0%)
Brown (2007)	Level I *Fair*	15 RCTs N=2098	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Tranexamic acid (IV) vs placebo	Stroke	RR 1.31 (0.59, 2.93)	*No difference* 0.51	*NR*
Later (2009)	Level II *Good*	1 RCT N=202	Adult patients undergoing first-time, non-complex cardiac surgery with CPB	Hospital – planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Stroke	1% vs 1%	*No difference* 1.00	*NR*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio; TIA, transient ischaemic attack.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between tranexamic acid and no tranexamic acid.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on morbidity (thrombosis)?		Evidence table ref[a]: POQ3.I8b.P5 (thromb)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which included data from up to 10 RCTs, one supportive Level I study (Kagoma 2009/good quality) , one supportive Level I/II study which included data from one RCT (McIlroy 2009/good-fair quality) and eight additional RCTs published since the pivotal review (Taghaddomi 209/fair quality; Alvarez 2008/fair quality; Elwatidy 2008/fair quality; Wong 2008/fair quality; Chen 2008/fair quality; Choi 2009/fair quality; Mayur 2007/poor quality; Sekhavat 2009/poor quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in analyses of any surgery or cardiac surgery for DVT or PE. Supportive evidence All studies showed no difference between tranexamic and no tranexamic acid.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 (for supportive evidence see Summary Table POQ3.I8b.P5 (thrombosis) Any surgery (DVT) – 1.9% vs 2.9%; RR 0.77 (0.37, 1.61); 10 RCTs (N=681) Any surgery (PE) – 0.4% vs 1.3%; RR 0.55 (0.17, 1.76); 7 RCTs (N=568) Cardiac surgery (DVT) – 0% vs 1.0%; RR 0.37 (0.04, 3.47); 2 RCTs (N=291) Cardiac surgery (PE) – 0% vs 0.7%; RR 0.33 (0.04, 3.15); 2 RCTs (N=289)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis of the pivotal review; a number of studies were in orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review included studies from a number of countries. Included RCTs were from a number of different countries including several from the Middle East and Asia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

The thrombosis outcome includes deep vein thrombosis, pulmonary embolism and outcomes that have been specified as thrombosis but not further defined in included studies.

Generalisability made a C as being applied to the whole surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study , one supportive Level I/II study and eight additional RCTs.
2. Consistency	A	There was no heterogeneity in the pivotal study. Other studies showed consistent results.
3. Clinical impact	D	There was no significant difference in any results but some of the risk estimates were large. Likely to be underpowered for thrombosis outcomes.
4. Generalisability	C	The results are generalisable to a surgical population; however, the majority of studies included in the pivotal and supportive Level I evidence were conducted in orthopaedic surgery.
5. Applicability	B	A moderate number of studies were conducted in a range of countries. The additional RCTs were conducted in Iran, Spain, Saudi Arabia, Canada, Taiwan, China and India. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on risk of thrombosis, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: DVT, deep vein thrombosis; PR, pulmonary embolism; RCT, randomised controlled trial; RR, risk ratio; SR, systematic review.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.P5 (thrombosis) Characteristics and results of studies examining the effect of tranexamic acid on morbidity (thrombosis)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	10 RCTs N=681	Adult patients undergoing any surgery	Hospital – planned surgery Unknown[c]	Tranexamic acid (IV) vs no tranexamic acid	DVT	RR 0.77 (0.37, 1.61)	*No difference* 0.49	None *Phet*=0.81 (I^2=0%)
Henry (2007)	Level I *Good*	7 RCTs N=568	Adult patients undergoing any surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	PE	RR 0.55 (0.17, 1.76)	*No difference* 0.31	None *Phet*=0.93 (I^2=0%)
Henry (2007)	Level I *Good*	2 RCTs N=114	Adult patients undergoing any surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	Other thrombosis	RR 2.10 (0.49, 8.99)	*No difference* 0.32	None *Phet*=0.80 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	2 RCTs N=291	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	DVT	RR 0.37 (0.04, 3.47)	*No difference* 0.38	None *Phet*=0.95 (I^2=0%)
Henry (2007)	Level I *Good*	2 RCTs N=289	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs no tranexamic acid	PE	RR 0.33 (0.04, 3.15)	*No difference* 0.34	None *Phet*=0.98 (I^2=0%)
McIlroy (2009)	Level I/II *Good/Fair*	1 RCT N=79	Adult patients receiving ASA undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Thrombotic complications	OR 0.32 (0.01, 8.02)	*No difference* 0.49	NA
Taghaddomi (2009)	Level II *Fair*	1 RCT N=100	Adult patients undergoing off-pump CABG surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Thrombosis	0% vs 0%	*No difference* NA	*NA*
Orthopaedic surgery									
Kagoma (2009)	Level I *Good*	10 RCTs N=459	Adult patients undergoing total hip or knee replacement surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	VTE	RD -0.01 (-0.04, 0.02)	*No difference* NR	NR
Alvarez (2008)	Level II *Fair*	1 RCT N=95	Adult patients undergoing total knee arthroplasty	Hospital – planned surgery Spain	Tranexamic acid (IV) vs placebo	Thrombosis	0% vs 0%	*No difference* NA	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
Elwatidy (2008)	Level II *Fair*	1 RCT N=64	Adult and paediatric patients undergoing spine surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (IV) vs placebo	Thrombosis	0% vs 0%	*No difference* NA	*NA*
Wong (2008)	Level II *Good*	1 RCT N=147	Adult patients undergoing spinal fusion surgery	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Thrombosis	0% vs 1%	*No difference* 1.00	*NA*
Other surgery									
Chen (2008)	Level II *Fair*	1 RCT N=55	Adult patients undergoing head and neck surgery	Hospital – planned surgery Taiwan	Tranexamic acid (IV) vs placebo	DVT	0% vs 0%	*No difference* NA	*NA*
Choi (2009)	Level II *Fair*	1 RCT N=61	Adult patients undergoing orthognathic surgery	Hospital – planned surgery China	Tranexamic acid (IV) vs placebo	Thrombosis	0% vs 0%	*No difference* NA	*NA*
Mayur (2007)	Level II *Poor*	1 RCT N=100	Adult patients undergoing caesarean section	Hospital – planned surgery India	Tranexamic acid (IV) vs placebo	Thrombosis	0% vs 0%	*No difference* NA	*NA*
Sekhavat (2009)	Level II *Poor*	1 RCT N=90	Adult patients undergoing caesarean section	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Thrombosis	0% vs 0%	*No difference* NA	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NA, not applicable; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on quality of life?		Evidence table ref[a]: POQ3.I8b.P6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies of any level were identified which assessed the effect of tranexamic acid on quality of life.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on quality of life, compared with no therapy, is unknown.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on re-operation for bleeding?		Evidence table ref[a]: POQ3.I8b.S2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from up to 18 RCTs, two supportive Level I studies (Henry 2009/good quality; Brown 2007/fair quality), one supportive Level I/II study which includes data from one RCT (McIlroy 2009/goog-fair quality) and three additional RCTs published since the pivotal review (Later 2009/good quality; Maddali 2007/good quality; Mehr-Aein 2007/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in main analyses Supportive evidence Results similar for Brown meta-analysis and additional RCTs.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – 2.9% vs 5.0%; RR 0.67 (0.41, 1.09); 18 RCTs (N=1598) Cardiac surgery – 2.7% vs 4.9%; RR 0.65 (0.39, 1.08); 17 RCTs (N=1540) Supportive evidence – Brown 2007 (see also Summary table POQ3.I8b.S2) Cardiac surgery – no absolute risks reported; RR 0.70 (0.44, 1.11); 21 RCTs (N=2255)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. Nearly all included evidence was in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review included studies from a wide range of countries. Included RCTs were from a number of different countries including The Netherlands, Oman and Iran.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study, one supportive Level I/II study and three additional RCTs.
2. Consistency	A	There was no heterogeneity in the pivotal study and the results of the supportive and additional studies were consistent.
3. Clinical impact	D	There was no difference in risk of re-operation; however, the included studies may be underpowered to detect a difference.
4. Generalisability	C	The results are generalisable to a cardiac surgical population.
5. Applicability	B	There were a reasonable number of studies conducted in a range of countries. The additional RCTs were conducted in The Netherlands, Oman and Iran. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of intravenous tranexamic acid therapy on risk of reoperation due to bleeding, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: RCT, randomised controlled trial; RR, risk ratio; SR, systematic review.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8b.S2 Characteristics and results of studies examining the effect of tranexamic acid on re-operation for bleeding

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	18 RCTs N=1598	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Re-operation for bleeding	RR 0.67 (0.41, 1.09)	*No difference* 0.11	*None* P*het*=0.92 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	17 trials N=1540	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Re-operation for bleeding	RR 0.65 (0.39, 1.08)	*No difference* 0.097	*None* P*het*=0.90 (I^2=0%)
Henry (2009)	Level I *Good*	NR NR	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs placebo	Re-operation for bleeding	RR 0.67 (0.41, 1.12)	*No difference* NR	*NR*
Brown (2007)	Level I *Fair*	21 RCTs N=2255	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	Tranexamic acid (IV) vs placebo	Return to operating room	RR 0.70 (0.44, 1.11)	*No difference* 0.125	*NR*
McIlroy(2009)	Level I/II *Good/Fair*	1 RCT N=79	Adult patients receiving ASA undergoing cardiac surgery	Hospital – planned surgery Unknown	Tranexamic acid (IV) vs placebo	Surgical re-exploration	OR 0.30 (0.01, 8.02)	*No difference* NR	*NA*
Later (2009)	Level II *Good*	1 RCT N=202	Adult patients undergoing first-time, non-complex cardiac surgery with CPB	Hospital – planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Re-operation for any reason	14% vs 14%	*No difference* 1.00	*NA*
						Re-operation for surgical bleeding	3% vs 3%	*No difference* 1.00	*NA*
						Re-operation for non-surgical bleeding	2% vs 4%	*No difference* 0.68	*NA*
Maddali (2007)	Level II *Good*	1 RCT N=222	Adult patients undergoing primary CABG surgery	Hospital – planned surgery Oman	Tranexamic acid (IV) vs placebo	Re-operation for bleeding	3% vs 3%	*No difference* NS	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adult patients undergoing primary CABG surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Re-exploration for bleeding	0% vs 3%	*No difference* >0.05	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (%) vs control (%)	*Significance* P-value	
ADULT POPULATION/TOPICAL TRANEXAMIC ACID									
Cardiac surgery									
Fawzy (2009)	Level II Good	1 RCT N=38	Adult patients undergoing primary isolated CABG surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (topical) vs placebo	Re-operation for bleeding	5% vs 0%	*No difference 1.00*	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiac pulmonary bypass; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence has been downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between tranexamic acid and no tranexamic acid.

Key question(s): In patients undergoing surgery, what is the effect of administration of tranexamic acid on hospital length of stay?		Evidence table ref[a]: POQ3.I8b.S5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) including data from up to 4 RCTs and eight additional RCTs published since the pivotal review (Jimenez 2007/good quality; Later 2009/good quality; Mehr-Aein 2007/good quality; Elwatidy 2008/fair quality; Sadeghi 2007/good quality; Wong 2008/good quality; Chen 2008/fair quality; Choi 2009/fair quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Some inconsistency between SR and individual RCTs. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in analyses. Supportive evidence No difference between tranexamic acid and no tranexamic acid in most supportive studies although in some cases the length of stay is slightly longer with tranexamic acid.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (days) – WMD -0.30 (-0.71, 0.10); 4 RCTs (N=176) Cardiac surgery (days) – WMD -0.23 (-0.67, 0.21); 2 RCTs (N=116) Supportive evidence – see Summary Table POQ3.I8b.S5	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. There is evidence available for a number of different surgery types.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review included studies from a wide range of countries. Included RCTs were from a number of different countries including several from the Middle East and Asia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Advisory Committee on Prescription Medicines (ACPM) has recently recommended approval of tranexamic acid injection "for the reduction of peri- and postoperative blood loss and of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee or hip arthroplasty; and paediatric patients undergoing cardiac surgery". Tranexamic acid tablets are approved in Australia for a number of indications including haemostatic, hereditary angioedema, short-term treatment of traumatic hyphaema, patients with coagulopathies undergoing minor surgery, and menorrhagia.

Consistency changed from A to D as some results went slightly in the opposite direction.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality) and eight additional RCTs.
2. Consistency	D	There was some inconsistency between studies with most studies showing no difference (although the direct was slightly different in some) and one study showing a significant difference in favour of tranexamic acid.
3. Clinical impact	D	There was no difference in length of hospital stay.
4. Generalisability	C	The results are generalisable to a surgical population.
5. Applicability	B	There were studies from a number of countries including Spain, The Netherlands, Iran, Saudi Arabia, Canada, Taiwan and Hong Kong. Likely to be applicable to the Australian setting. .

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy does not appear to affect hospital length of stay compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: RCT, randomised controlled trial; SR, systematic review; WMD, weighted mean difference.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission.

POQ3.I8b.S5 Characteristics and results of studies examining the effect of tranexamic acid on hospital length of stay

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
ADULT POPULATION/IV TRANEXAMIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	4 RCTs N=176	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	Tranexamic acid (IV) vs no tranexamic acid	Hospital length of stay (days)	WMD -0.30 (-0.71, 0.10)	*No difference* 0.14	*None* P*het*=0.66 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	2 RCTs N=116	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	Tranexamic acid (IV) vs no tranexamic acid	Hospital length of stay (days)	WMD -0.23 (-0.67, 0.21)	*No difference* 0.31	*None* P*het*=0.64 (I^2=0%)
Jimenez (2007)	Level II *Good*	1 RCT N=50	Adult patients undergoing CPB surgery	Hospital – planned surgery Spain	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	4.5 vs 4	*No difference* 0.34	*NA*
Later (2009)	Level II *Good*	1 RCT N=202	Adult patients undergoing first-time, non-complex cardiac surgery with CPB	Hospital – planned surgery The Netherlands	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	9.4 vs 8.5	*No difference* 0.43	*NA*
Mehr-Aein (2007)	Level II *Good*	1 RCT N=66	Adult patients undergoing primary CABG surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	4.8 vs 4.8	*No difference* 0.09	*NA*
Orthopaedic surgery									
Elwatidy (2008)	Level II *Fair*	1 RCT N=64	Adult and paediatric patients undergoing spine surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	8.5 vs 10.7	*No difference* 0.21	*NA*
Sadeghi (2007)	Level II *Good*	1 RCT N=67	Adult patients undergoing hip fracture surgery	Hospital – planned surgery Iran	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	4.3 vs 5.8	*Favours tranexamic acid* <0.05	*NA*
Wong (2008)	Level II *Good*	1 RCT N=147	Adult patients undergoing spinal fusion surgery	Hospital – planned surgery Canada	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	9.2 vs 8.5	*No difference* 0.38	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or TXA (mean) vs control (mean)	*Significance* P-value	
Other surgery									
Chen (2008)	Level II *Fair*	1 RCT N=55	Adults undergoing head and neck surgery	Hospital – planned surgery Taiwan	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	4.8 vs 5.3	No difference 0.087	*NA*
Choi (2009)	Level II *Fair*	RCT N=61	Adults undergoing orthognathic surgery	Hospital – planned surgery Hong Kong	Tranexamic acid (IV) vs placebo	Hospital length of stay (days)	7.2 vs 7.5	No difference 0.32	*NA*
ADULT POPULATION/TOPICAL TRANEXAMIC ACID									
Cardiac surgery									
Fawzy (2009)	Level II Good	1 RCT N=38	Adult patients undergoing primary isolated CABG surgery	Hospital – planned surgery Saudi Arabia	Tranexamic acid (topical) vs placebo	Hospital length of stay (days)	7.5 vs 7.8	No difference 0.68	*NA*
ADULT POPULATION/ORAL TRANEXAMIC ACID									
Liver surgery									
Gurusamy (2009)	Level I/II *Good/Fair*	1 RCT N=214	Adult patients undergoing liver resection	Hospital – planned surgery China	Tranexamic acid (oral) vs placebo	Hospital length of stay (days)	8 vs 9	*No difference* 0.34	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence has been downgraded to Level II.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between tranexamic acid and no tranexamic acid.

Recommendation(s) for administration of tranexamic acid

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In adult patients undergoing cardiac surgery, the use of intravenous tranexamic acid is recommended.	A	PO3.I8b.P1, PO3.I8b.P2, PO3.I8b.P3, PO3.I8b.P5
In adult patients undergoing non-cardiac surgery, if substantial blood loss is anticipated, the use of intravenous tranexamic acid is recommended.	B	PO3.I8b.P1, PO3.I8b.P2, PO3.I8b.P3, PO3.I8b.P5

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Increased use of tranexamic acid.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Drug cost (albeit modest).		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Potential resistance.		
What could help to facilitate implementation of the recommendation?	YES	NO
Education; promotion of PO guideline.		

Intervention 8 – Administration of antifibrinolytics & DDAVP: ε-aminocaproic acid

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on transfusion incidence?		Evidence table ref[a]: POQ3.I8c.P1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from up to 14 RCTs and two supportive Level I studies (Brown 2007/fair quality; Kagoma 2009/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 Moderate to substantial heterogeneity between studies. May be due to different surgery types assessed. Only one study available for liver surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – 33.3% vs 45.1%; RR 0.75 (0.58, 0.96); 14 RCTs (N=801) Cardiac surgery – 26.2% vs 39.8%; RR 0.65 (0.47, 0.91); 10 RCTs (N=597) Orthopaedic surgery – 33.9% vs 36.5%; RR 0.96 (0.61, 1.50); 3 RCTs (N=122) Liver surgery – 85.7% vs 92.5%; RR 0.93 (0.80, 1.08); 1 RCT (N=82) Supportive evidence –see Summary Table POQ3.I8c.P1	A	Very large
	B	Substantial (cardiac)
	C	Moderate
	D	Underpowered (non-cardiac)
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery. There were also subgroup analyses of patients who had undergone surgery with/without a transfusion protocol.	A	Evidence directly generalisable to target (cardiac) population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target (non-cardiac) population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

The Henry (pivotal) review assessed quality and performed a subgroup analysis of transfusion incidence for all surgery types based on the rating (A,B or C) of treatment allocation[b]. The analysis showed no substantial difference in the results between studies rated A, B or C, with the exception that potentially poorer studies showed less effect.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Cardiac	Other	Description
1. Evidence base	A	A	There is one pivotal Level I study (good quality) and two supportive Level I studies.
2. Consistency	B	B	Most studies were reasonably consistent with differences mostly related to magnitude of effect rather than direction of effect. Differences may be related to surgery type.
3. Clinical impact	B	D	There was a significant difference for cardiac surgery only. There was no difference for non-cardiac surgery (predominantly orthopaedic surgery) but includes few studies so may be underpowered to detect a difference.
4. Generalisability	A	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, intravenous ε-aminocaproic acid therapy reduces the incidence of allogeneic blood transfusion compared with no therapy. In adult patients undergoing non-cardiac surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on the incidence of allogeneic transfusion, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[b] Cochrane ratings defined as follows: Grade A, adequate allocation concealment; Grade B, uncertain allocation concealment; Grade C, inadequate allocation concealment.

POQ3.I8c.P1 Characteristics and results of studies examining the effect of **ε**-aminocaproic acid on transfusion incidence.

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV **E**-AMINOCAPROIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	14 RCTs N=801	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion incidence (allogeneic blood)	RR 0.75 (0.58, 0.96)	*Favours ε-aminocaproic acid* 0.023	*Moderate* *Phet*=0.03 (I^2=47%)
Henry (2007)	Level I *Good*	13 RCTs N=771	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid with transfusion protocol	Transfusion incidence (allogeneic blood)	RR 0.73 (0.56, 0.95)	*Favours ε-aminocaproic acid* 0.019	*Substantial* *Phet*=0.02 (I^2=52%)
	Level I/II *Good/Fair*	1 RCT N=30	Adult patients undergoing any surgery (orthopaedic surgery only)	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid without transfusion protocol	Transfusion incidence (allogeneic blood)	RR 1.33 (0.36, 4.97)	*No difference* 0.67	*NA*
Henry (2007)	Level I *Good* Rating A[d]	3 RCTs N=218	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion incidence (allogeneic blood)	RR 0.68 (0.44, 1.04)	*No difference* 0.076	*Moderate* *Phet*=0.25 (I^2=29%)
	Level I *Good* Rating B[d]	9 RCTs N=455	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion incidence (allogeneic blood)	RR 0.68 (0.46 1.03)	*No difference* 0.068	*Moderate* *Phet*=0.13 (I^2=36%)
	Level I *Good* Rating C[d]	2 RCTs N=128	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion incidence (allogeneic blood)	RR 0.93 (0.81, 1.08)	*No difference* 0.35	*None* *Phet*=0.72 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	10 RCTs N=597	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion incidence (allogeneic blood)	RR 0.65 (0.47, 0.91)	*Favours ε-aminocaproic acid* 0.011	*Moderate* *Phet*=0.11 (I^2=38%)
Brown (2007)	Level I *Fair*	10 RCTs N=628	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Transfusion incidence (pRBCs)	RR 0.63 (0.44, 0.90)	*Favours ε-aminocaproic acid* 0.010	*NR*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
Orthopaedic surgery									
Henry (2007)	Level I *Good*	3 RCTs N=122	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion incidence (allogeneic blood)	RR 0.96 (0.61, 1.50)	*No difference* 0.85	*None* *Phet*=0.64 (I^2=0%)
Kagoma (2009)	Level I *Good*	3 RCTs N=180	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Transfusion incidence	RR 0.64 (0.21, 1.93)	*No difference* NR	*NR*
Liver surgery									
Henry (2007)	Level I/II *Good/Fair*	1 RCT N=82	Adult patients undergoing liver surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion incidence (allogeneic blood)	RR 0.93 (0.80, 1.08)	*No difference* 0.33	*NA*
PAEDIATRIC POPULATION/IV E-AMINOCAPROIC ACID									
Orthopaedic surgery									
Tzortzopoulou (2008)	Level I/II *Good/Good*	1 RCT N=36	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Transfusion incidence	RR 1.04 (0.69, 1.57)	*No difference* 0.84	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; pRBC, packed red blood cell; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between ε-aminocaproic acid and no ε-aminocaproic acid.
[d] Cochrane ratings defined as follows: Grade A, adequate allocation concealment; Grade B, uncertain allocation concealment; Grade C, inadequate allocation concealment.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on transfusion volume?		Evidence table ref[a]: POQ3.I8c.P2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from up to 4 RCTs and one additional RCT (Berenholtz 2009/good quality) in major spine surgery (conducted in the US).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results somewhat inconsistent. Likely to be due to differences in reporting of results in pivotal review and supportive studies (ie, includes all patients or transfused patients only; different blood products assessed; different transfusion units included such as units or mL). Pivotal evidence – Henry 2007 Significant heterogeneity in analysis of transfusion volume for all patients but not for transfusion volume including only transfused patients. Supportive evidence –Mix of results showing effect favouring ε-ACA and no difference.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (all patients; units) – WMD -1.77 (-2.59, -0.95); 4 RCTs (N=198) Any surgery (transfused patients; units) – WMD 0.22 (-0.34, 0.79); 3 RCTs (N=119) Supportive evidence – (see Summary Table POQ3.I8d.P2)	A	Very large
	B	Substantial
	C	Moderate
	D	Inconsistent
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. The majority of studies were in cardiac or orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a range of countries. The additional RCT was conducted in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently listed for use in Australia.

Generalisability rated C as most evidence in a restricted surgical population but applied to general surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality) and one additional RCT.
2. Consistency	C	There are some inconsistencies depending on the denominator used (all patients vs transfused patients), surgery type and blood products.
3. Clinical impact	D	There was generally significantly less transfusion when all patients were included in the analysis; however, there was no significant difference when only transfused patients were considered. .
4. Generalisability	C	The results are generalisable to a surgical population; in particular those undergoing cardiac and orthopaedic surgery.
5. Applicability	C	Studies were conducted in a number of countries. The additional RCT was conducted in the US. Possibly applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on volume of allogeneic blood transfusion compared with no therapy is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: ACA, aminocaproic acid; CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.P2 Characteristics and results of studies examining the effect of **ε**-aminocaproic acid on transfusion volume

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV E-AMINOCAPROIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	4 RCTs N=198	Adult patients undergoing any surgery (all patients)	Hospital – planned surgery Various countries[c]	ε -aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion volume (units; allogeneic blood)	WMD -1.77 (-2.59, -0.95)	*Favours ε-aminocaproic acid* <0.001	*Substantial* Phet=0.02 (I^2=69%)
		3 RCTs N=119	Adult patients undergoing any surgery (transfused patients only)	Hospital – planned surgery Various countries	ε -aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion volume (units; allogeneic blood)	WMD 0.22 (-0.34, 0.79)	*No difference* 0.44	*None* Phet=0.76 (I^2=0%)
Orthopaedic surgery									
Berenholtz (2009)	Level II *Good*	1 RCT N=182	Adult patients undergoing major spine surgery (all patients)	Hospital – planned surgery US	ε -aminocaproic acid (IV) vs placebo	Transfusion volume (units; total allogeneic RBC)	MD -1.00 (-2.47, 0.47)[d]	*No difference* 0.18[d]	*NA*
						Transfusion volume (units; postoperative RBC)	MD -0.80 (-1.48, -0.12)[d]	*Favours ε-aminocaproic acid* 0.02[d]	*NA*
						Transfusion volume (units; total FFP)	MD -0.70 (-2.17, 0.77)[d]	*No difference* 0.35[d]	*NA*
						Transfusion volume (units; total platelets)	MD 0.00 (-1.17, 1.17)[d]	*No difference* 1.00[d]	*NA*
						Transfusion volume (units; total all blood products)	MD -2.60 (-6.38, 1.18)[d]	*No difference* 0.18[d]	*NA*
PAEDIATRIC POPULATION/IV E-AMINOCAPROIC ACID									
Cardiac surgery									
Schouten (2009)	Level I *Good*	3 RCTs N=410	Paediatric patients undergoing cardiac surgery	Hospital – planned surgery Unknown	ε -aminocaproic acid (IV) vs no ε-aminocaproic acid	Transfusion volume (mL/kg; plasma)	WMD -3 (-5, -1)	*Favours ε-aminocaproic acid* NR	*None* Phet=NR (I^2=20%)
Orthopaedic surgery									
Tzortzopoulou (2008)	Level I/II *Good/Good*	1 RCT N=87	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	ε -aminocaproic acid (IV) vs placebo	Transfusion volume (mL)	WMD -245 (-481, -8.97)	*Favours ε-aminocaproic acid* 0.042	*NA*

Note: Studies/analyses providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies/analyses provide supportive evidence.
Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; *het*, heterogeneity; IV, intravenous; MD, mean difference; NA, not applicable; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; SMD, standardised mean difference; US, United States of America; WMD; weighted mean difference.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between ε-aminocaproic acid and no ε-aminocaproic acid.
[d] Post-hoc calculation for this summary.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on blood loss?		Evidence table ref[a]: POQ3.I8c.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) including data from up to 12 RCTs, three supportive Level I studies (Brown 2007/fair quality; Kagoma 2009/good quality; McIlroy 2009/good quality [which combined data for TXA and ACA) and two additional RCTs (Gharebaghian 2006/fair quality; Berenholtz 2009/good quality) published since the pivotal review.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses and RCTs. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 Moderate to substantial heterogeneity (see note) in main analyses. No heterogeneity in analyses by surgery type. Some inconsistency between non-cardiac surgery types.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained (cardiac)
	C	Some inconsistency, reflecting genuine uncertainty around question (orthopaedic)
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery (intraoperative blood loss) – WMD -142 (-285, 0.92); 4 RCTs (N=171) Any surgery (postoperative blood loss) – WMD -202 (-274, -131); 12 RCTs (N=940) Cardiac surgery (intraoperative blood loss) – WMD -214 (-310, -117); 2 RCTs (N=79) Cardiac surgery (postoperative blood loss) – WMD -196 (-272, -121); 11 RCTs (N=894) Orthopaedic surgery (postoperative blood loss) – WMD -276 (-449, -103); 1 RCT (N=46)	A	Very large
	B	Substantial (cardiac)
	C	Moderate (orthopaedic)
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac and orthopaedic surgery. There was also evidence relating to adults undergoing cardiac surgery who had received aspirin.	A	Evidence directly generalisable to target population (cardiac)
	B	Evidence directly generalisable to target population with some caveats (orthopaedic)
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a wide range of countries. Additional RCTs were conducted in Iran and the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats (cardiac surgery)
	C	Evidence probably applicable to Australian healthcare context with some caveats (orthopaedic surgery)
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Cardiac	Ortho	Description
1. Evidence base	A	A	There is one pivotal Level I study (good quality), three supportive Level I studies and two additional RCTs.
2. Consistency	B	C	Results were generally consistent. Substantial heterogeneity in any surgery analysis may be due to surgery types.
3. Clinical impact	B	C	There was generally significantly less blood loss with ACA, particularly postoperatively. This was strongest in cardiac surgery.
4. Generalisability	A	B	Results generalisable to an adult surgical population; in particular those undergoing cardiac and orthopaedic surgery.
5. Applicability	B	C	Studies were conducted in a number of countries. The additional RCTs were conducted in the US and Iran. Possibly applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, intravenous ε-aminocaproic acid therapy reduces blood loss compared with no therapy.

In adult patients undergoing major orthopaedic surgery, intravenous ε-aminocaproic acid therapy may reduce blood loss compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: ACA, ε-aminocaproic acid; CI, confidence interval, RBC, red blood cell; RCT, randomised controlled trial; TXA, tranexamic acid.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.P3 Characteristics and results of studies examining the effect of **ε**-aminocaproic acid on blood loss

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or **ε**-ACA (mean) vs control (mean)	*Significance* P-value	
ADULT POPULATION/IV **E**-AMINOCAPROIC ACID									
Any surgery									
Henry (2007)	Level I *Good*	4 RCTs N=171	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Intraoperative blood loss (mL)	WMD -142 (-285, 0.92)	*No difference* 0.051	*Moderate* P*het*=0.19 (I^2=37%)
		12 RCTs N=940	Adult patients undergoing any surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Postoperative blood loss (mL)	WMD -202 (-274, -131)	*Favours ε-aminocaproic acid* <0.001	*Substantial* P*het*<0.001 (I^2=89%)
Cardiac surgery									
Henry (2007)	Level I *Good*	2 RCTs N=79	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Intraoperative blood loss (mL)	WMD -214 (-310, -117)	*Favours ε-aminocaproic acid* <0.001	*None* P*het*=0.73 (I^2=0%)
		11 RCTs N=894	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Postoperative blood loss (mL)	WMD -196 (-272, -121)	*Favours ε-aminocaproic acid* <0.001	*Substantial* P*het*<0.001 (I^2=89%)
Brown (2007)	Level I Fair	3 RCTs N=144	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Total blood loss (mL)	WMD -240 (-341, -140)	*Favours ε-aminocaproic acid* <0.001	*NR*
McIlroy(2009)	Level I *Good*	3 RCTs N=259	Adult patients receiving ASA undergoing cardiac surgery	Hospital – planned surgery Unknown	Lysine analogues[h] (IV) vs placebo	Postoperative chest tube blood loss (mL)	WMD -189 (-287, -91)	*Favours lysine analogues* <0.001	*Substantial* P*het*=0.05 (I^2=67%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or ε-ACA (mean) vs control (mean)	*Significance* P-value	
Gharebaghian (2006)	Level II *Fair*	1 RCT N=60	Adult patients undergoing major CABG surgery	Hospital – planned surgery Iran	E-aminocaproic acid (IV) pre-incision regimen[d] vs placebo	Chest tube blood loss at 6 hrs (mL)	~ 300 vs ~ 600	*Favours ε-aminocaproic acid* <0.05	*NA*
						Chest tube blood loss at 12 hrs (mL)	~500 vs ~650	*No difference* >0.05	*NA*
						Chest tube blood loss at removal (mL)	~1000 vs ~2000	*Favours ε-aminocaproic acid* <0.05	*NA*
					E-aminocaproic acid (IV) post-heparin regimen[e] vs placebo	Chest tube blood loss at 6 hrs (mL)	~ 300 vs ~ 600	*Favours ε-aminocaproic acid* <0.05	*NA*
						Chest tube blood loss at 12 hrs (mL)	~500 vs ~650	*No difference* >0.05	*NA*
						Chest tube blood loss at removal (mL)	~800 vs ~2000	*Favours ε-aminocaproic acid* <0.05	*NA*
Orthopaedic surgery									
Henry (2007)	Level I *Good*	2RCTs N=92	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Total blood loss (mL)	WMD -300 (-523, -77)	*Favours ε-aminocaproic acid* 0.0084	*None* P*het*=0.39 (I^2=0%)
						Intraoperative blood loss (mL)	WMD 10.9 (-260, 282)	*No difference* 0.94	*None* P*het*=0.26 (I^2=22%)
	Level I/II *Good/Fair*	1 RCT N=46	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Postoperative blood loss (mL)	WMD -276 (-449, -103)	*Favours ε-aminocaproic acid* 0.0017	*NA*
Kagoma (2009)	Level I *Good*	3 RCTs N=141	Adults undergoing total knee or hip replacement	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Total bleeding[f] (mL)	WMD -331 (-544, -118)	*Favours ε-aminocaproic acid* P<0.05	*NR*
Berenholtz (2009)	Level II Good	1 RCT N=182	Adult patients undergoing major spine surgery	Hospital – planned surgery US	E-aminocaproic acid (IV) vs placebo	Intraoperative blood loss (mL)	MD -335 (-990, 320)[g]	*No difference* 0.32[g]	*NA*
						Post-surgical to POD 1 blood loss (mL)	MD -430 (-1121, 261)[g]	*No difference* 0.22[g]	*NA*

Study	Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI) or ε-ACA (mean) vs control (mean)	*Significance* P-value	
PAEDIATRIC POPULATION/IV E-AMINOCAPROIC ACID									
Orthopaedic surgery									
Schouten (2009)	Level I/II *Good/Good*	1 RCT[i] N=36	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Blood loss (mL/kg/day)	WMD -59 (-262, 144)	*No difference* NR	*NA*
Tzortzopoulou (2008)	Level I/II *Good/Good*	1 RCT[i] N=36	Paediatric patients undergoing scoliosis surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Total blood loss (mL)	WMD -325 (-587, -63)	*Favours ε-aminocaproic acid* 0.015	*NA*
ADULT POPULATION/TOPICAL E-AMINOCAPROIC ACID									
Other surgery									
Athanasiadis (2007)	Level II *Fair*	1 RCT N=20	Adult patients undergoing endoscopic sinus surgery	Hospital – planned surgery Australia	E-aminocaproic acid (topical) vs placebo	Bleeding grading scales[i] at 0, 2, 4, 6, 8 and 10 mins	NR	*No difference* NR	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; mL, millilitres; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SMD, standardised mean difference; WMD, weighted mean difference.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[d] The pre-incision group received 150 mg/kg ε-ACA over 10 mins as pre-incision bolus, followed by 15 mg/kg/hr as post-incision infusion and normal saline for post-heparin and 15 mg/kg/hr ε-ACA as 3 min following heparin to the end of CPB infusion.
[e] The post-heparin group received normal saline in pre-incision and post-incision and ε-ACA comprising 150 mg/kg over 10 mins after heparin injection followed by 15 mg/kg/hr ε-ACA from 3 mins following heparin injection to the end of CPB.
[f] Total bleeding measured intraoperatively by weighing surgical sponges, postoperatively through drainage or perioperatively through the haemoglobin balance method which measures blood loss through comparison or pre- and postoperative haemoglobin concentrations (haematoma volumes as well as hidden or internal blood loss were excluded).
[g] Calculated post-hoc for this Guideline.
[h] Includes ε-aminocaproic acid (2 RCTs) and tranexamic acid (1 RCT).
[i] These two reviews included the same study (Florentino 2004).[5]
[i] Wormald grading scale and Boezaart grading scale.

[5] Florentino-Pineda et al (2004) The effect of amicar on perioperative blood loss in idiopathic scoliosis: the results of a prospective, randomized double-blind study. Spine 29: 233-238.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on mortality?		Evidence table ref[a]: POQ3.I8c.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from up to 5 RCTs, one supportive Level I study (Brown 2007/fair quality) and one additional RCT (Berenholtz 2009/good quality) in major spine surgery conducted in the US.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in main analysis and cardiac surgery analysis.	A	All studies consistent in finding no significant difference
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Any surgery – 2.6% vs 1.9%; RR 1.17 (0.47, 2.93); 5 RCTs (N=714) Cardiac surgery – 2.0% vs 0.9%; RR 1.65 (0.50, 5.43); 4 RCTs (N=632) Supportive evidence – Brown 2007 Cardiac surgery – absolute risk not reported; RR 1.82 (0.55, 5.98); 6 RCTs (N=735) See also Summary Table POQ3.I8c.P4	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a range of countries. An additional RCT was conducted in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

Generalisability rated C as most evidence in a restricted surgical population but applied to general surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study and one additional RCT.
2. Consistency	A	There was no heterogeneity in the pivotal Level I study. All studies showed no significant difference.
3. Clinical impact	D	Results show a slightly increased risk with no significant difference (7/346 versus 3/326 in cardiac surgery) but studies likely underpowered to detect a difference in mortality.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. The additional RCT was conducted in the US. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery, the effect of intravenous ε-aminocaproic acid therapy on mortality compared with no therapy is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.P4 Characteristics and results of studies examining the effect of **ε**-aminocaproic acid on mortality

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV E-AMINOCAPROIC ACID									
Henry (2007)	Level I *Good*	5 RCTs N=714	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Mortality	RR 1.17 (0.47, 2.93)	*No difference* 0.73	*None* P*het*=0.78 (I^2=0%)
Cardiac surgery									
Henry (2007)	Level I *Good*	4 RCTs N=632	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Mortality	RR 1.65 (0.50, 5.43)	*No difference* 0.41	*None* P*het*=0.81 (I^2=0%)
Brown (2007)	Level I Fair	6 RCTs N=735	Adult patients undergoing cardiac surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Mortality	RR 1.82 (0.55, 5.98)	*No difference* 0.32	*NR*
Orthopaedic surgery									
Berenholtz (2009)	Level II *Good*	1 RCT N=182	Adults undergoing major spine surgery	Hospital – planned surgery US	E-aminocaproic acid (IV) vs placebo	In-hospital mortality	RR 0.30 (0.01, 8.08)[d]	*No difference* 0.50[d]	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between ε-aminocaproic acid and no ε-aminocaproic acid.
[d] Post-hoc analysis conducted for this guideline.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on morbidity (myocardial infarction)?		Evidence table ref[a]: POQ3.I8c.P5 (MI)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from up to 4 RCTs, one supportive Level I study (Brown 2007/fair quality) and one additional RCT conducted in the US.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results generally consistent between pivotal and supportive meta-analyses, however there is a slight difference in direction of effect. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in cardiac surgery analysis.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Cardiac surgery– 3.5% vs 4.3%; RR 0.89 (0.37, 2.18); 4 RCTs (N=632) Supportive evidence – Brown 2007 Cardiac surgery – absolute risk not reported; RR 1.14 (0.50, 2.60); 8 RCTs (N=839)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. Only cardiac surgery was included in the systematic reviews. There was one RCT in orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

Generalisability rated C as most evidence in a restricted surgical population but applied to general surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study and one additional RCT.
2. Consistency	B	No heterogeneity in the pivotal study. Small difference in direction of effect between the pivotal and supportive Level I studies. There were no events in the additional RCT.
3. Clinical impact	D	There was no significant difference in the analyses; however, the studies are likely to be underpowered to detect a difference.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. The additional RCT was conducted in the US. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on the risk of myocardial infarction, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.P5 (MI) Characteristics and results of studies examining the effect of ε-aminocaproic acid on morbidity (myocardial infarction)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV E-AMINOCAPROIC ACID									
Cardiac surgery									
Henry (2007)	Level I *Good*	4 RCTs N=632	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Myocardial infarction	RR 0.89 (0.37, 2.18)	*No difference* 0.80	*None* P*het*=0.33 (I^2=12%)
Brown (2007)	Level I *Fair*	8 RCTs N=839	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	E-aminocaproic acid (IV) vs placebo	Myocardial infarction	RR 1.14 (0.50, 2.60)	*No difference* 0.76	*NR*
Orthopaedic surgery									
Berenholtz (2009)	Level II *Good*	1 RCT N=182	Adult patients undergoing major spine surgery	Hospital – planned surgery US	E-aminocaproic acid (IV) vs placebo	Myocardial infarction	NA[d]	*No difference* NA	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between ε-aminocaproic acid and no ε-aminocaproic acid.
[d] There were no myocardial infarctions in either treatment group.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on morbidity (stroke)?		Evidence table ref[a]: POQ3.I8c.P5 (stroke)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) which includes data from 3 RCTs, one supportive Level I study (Brown 2007/fair quality) and one additional RCT (Berenholtz 2009/good quality) in major spine surgery, conducted in the US.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in main analysis.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Cardiac surgery – 0.6% vs 0.9%; RR 0.59 (0.10, 3.44); 3 RCTs (N=541) Supportive evidence – Brown 2007 Cardiac surgery – absolute risk not reported; RR 0.60 (0.13, 2.81); 8 RCTs (N=833)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. Only cardiac surgery was included in the systematic reviews. There was one RCT in orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a wide range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

Generalisability rated C as most evidence in a restricted surgical population but applied to general surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I study and one additional RCT.
2. Consistency	A	There was no heterogeneity in the pivotal Level I study. Similar results were seen in the supportive Level I study and the additional RCT.
3. Clinical impact	D	There was no significant difference in the analyses; however, the studies are likely to be underpowered to detect a difference in stroke.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. The additional RCT was conducted in the US. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on risk of stroke, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8a.P5 (stroke) Characteristics and results of studies examining the effect of **ε**-aminocaproic acid on morbidity (stroke)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV E-AMINOCAPROIC ACID									
Cardiac surgery									
Henry (2007)	Level I *Good*	3 RCTs N=541	Adult patients undergoing cardiac surgery	Hospital – planned surgery Various countries[c]	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Stroke	RR 0.59 (0.10, 3.44)	*No difference* 0.55	*None* *Phet*=0.47 (I^2=0%)
Brown (2007)	Level I *Fair*	8 RCTs N=833	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	E-aminocaproic acid (IV) vs placebo	Stroke	RR 0.60 (0.13, 2.81)	*No difference* 0.52	*NR*
Orthopaedic surgery									
Berenholtz (2009)	Level II *Good*	1 RCT N=182	Adults undergoing major spine surgery	Hospital – planned surgery US	E-aminocaproic acid (IV) vs placebo	Cerebral infarction/TIA	RR 0.30 (0.01, 8.08)[d]	*No difference* 0.50 [d]	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio; TIA, transient ischaemic attack.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between ε-aminocaproic acid and no ε-aminocaproic acid.
[d] Post-hoc analysis conducted for this guideline.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on morbidity (thrombosis)?		Evidence table ref[a]: POQ3.I8c.P5 (thromb)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There was one pivotal Level I/II study (Henry 2007/good quality) which included data from only one small good quality RCT for orthopaedic surgery and one small fair quality RCT for liver surgery, one supportive Level I study (Kagoma 2009/good quality) which included data from three RCTs and one additional RCT (Berenholtz 2009/good quality) in major spine surgery conducted in the US. .	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Most evidence in orthopaedic surgery. Results consistent across systematic reviews and RCTs.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Orthopaedic surgery (DVT) – 5.1% vs 4.8%; RR 1.09 (0.25, 4.85); 1 RCT (N=46) Orthopaedic surgery (PE) – 0% vs 2.1%; RR 0.36 (0.02, 8.46); 1 RCT (N=46) Liver surgery (other thrombosis) – 4.8% vs 5.0%; RR 0.95 (0.14, 6.44); 1 RCT (N=82) Supportive evidence – Kagoma 2009 (see also Summary Table POQ3.18c.P5 (thrombosis) Orthopaedic surgery (VTE) - 0% vs 0%; RD 0.00 (-0.07, 0.07); 3 RCTs (N=180)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. Most of the evidence is in orthopaedic surgery. There was one RCT with evidence in liver surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in number of countries. The additional RCT was conducted in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

Generalisability rated C as most evidence in a restricted surgical population but applied to general surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	There was one pivotal Level I study (good quality) which included data from only one small good quality RCT, one supportive Level I study (which included three RCTs) and one additional RCT.
2. Consistency	A	Results similar suggesting potentially no difference or less risk with ε-aminocaproic acid.
3. Clinical impact	D	There was no significant difference in the analyses; however, studies likely to be underpowered to detect a difference.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing orthopaedic surgery
5. Applicability	C	A small number of studies were conducted in a range of countries. The additional RCT was conducted in the US. Possibly applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on risk of venous thromboembolism, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.P5 (thrombosis) Characteristics and results of studies examining the effect of ε-aminocaproic acid on morbidity (thrombosis)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV Ε-AMINOCAPROIC ACID									
Orthopaedic surgery									
Henry (2007)	Level I/II *Good/Good*	1 RCT N=46	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Deep vein thrombosis	RR 1.09 (0.25, 4.85)	*No difference* 0.91	*NA*
						Pulmonary embolism	RR 0.36 (0.02, 8.46)	*No difference* 0.53	*NA*
Kagoma (2009)	Level I *Good*	3 RCTs N=180	Adults undergoing orthopaedic surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	VTE complications	RD 0.00 (-0.07, 0.07)	*No difference* NR	*NR*
Berenholtz (2009)	Level II *Good*	1 RCT N=182	Adult patients undergoing major spine surgery	Hospital – planned surgery US	E-aminocaproic acid (IV) vs placebo	Deep vein thrombosis	RR 0.20 (0.01, 4.11)[c]	*No difference* 0.30[c]	*NA*
						Pulmonary embolism	RR 0.33 (0.04, 3.15)[c]	*No difference* 0.34 [c]	*NA*
						Any thrombotic complication	RR 0.33 (0.07, 1.61)[c]	*No difference* 0.17 [c]	*NA*
Liver surgery									
Henry (2007)	Level I/II *Good/Fair*	1 RCT N=82	Adult patients undergoing liver transplant	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Other thrombosis (not MI, stroke, DVT or PE)	RR 0.95 (0.14, 6.44)	*No difference 0.96*	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; IV, intravenous; MI, myocardial infarction; NA, not applicable; NR, not reported; PE, pulmonary embolism; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Post-hoc analysis for this guideline.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on quality of life?		Evidence table ref[a]: POQ3.I8c.P6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies of any level were identified which assessed the effect of ε-aminocaproic acid on quality of life.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently listed for use in Australia.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on quality of life, compared with no therapy, is unknown.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on re-operation for bleeding?		Evidence table ref[a]: POQ3.I8c.S2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Henry 2007/good quality) including data from 5 RCTs, one supportive Level I study (Brown 2007/fair quality), one supportive Level I/II study which includes data from one poor quality RCT (McIlroy 2009/good quality) and one additional RCT in major spine surgery (Berenholtz 2009/good quality) published since the pivotal review and conducted in the US.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Henry 2007 No significant heterogeneity (see note) in main analysis.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Cardiac surgery – 0.8% vs 3.3%; RR 0.35 (0.11, 1.17); 5 RCTs (N=740) Supportive evidence – Brown 2007 Cardiac surgery (return to operating room) – absolute risk not reported; RR 0.51 (0.15, 1.82); 9 RCTs (N=851)	A	Very large
	B	Substantial (potential)
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. Evidence was predominantly in cardiac surgery although there was one RCT in orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review states that studies were conducted in a range of countries.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (good quality), one supportive Level I studies, one supportive Level I/II study (including 1 RCT only) and one additional RCT (major spine surgery).
2. Consistency	A	There was no heterogeneity in the pivotal study and the results of the supportive and additional studies were consistent.
3. Clinical impact	B	There was no significant difference in the analyses but potentially substantial if trend upheld by greater powering.
4. Generalisability	A	The results are generalisable to an adult cardiac surgical population.
5. Applicability	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of intravenous ε-aminocaproic acid therapy on risk of reoperation for bleeding, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, Pot, potential; RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[b] Potentially substantial if results upheld in studies with greater power

POQ3.I8c.S2 Characteristics and results of studies examining the effect of **ε**-aminocaproic acid on re-operation for bleeding

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV E-AMINOCAPROIC ACID									
Cardiac surgery									
Henry (2007)	Level I *Good*	5 RCTs N=662	Adult patients undergoing any surgery	Hospital – planned surgery Various countries[c]	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Reoperation for bleeding	RR 0.35 (0.11, 1.17)	*No difference* 0.087	*None* P*het*=0.78 (I^2=0%)
Brown (2007)	Level I *Fair*	9 RCTs N=851	Adult patients undergoing cardiac surgery	Hospital – planned surgery Countries not specified	E-aminocaproic acid (IV) vs placebo	Return to operating room	RR 0.51 (0.15, 1.82)	*No difference* 0.30	*NR*
McIlroy(2009)	Level I/II *Good/Poor*	1 RCT N=30	Adult patients receiving ASA undergoing cardiac surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs placebo	Surgical re-exploration	OR 0.31 (0.01, 8.28)	*No difference* NR	*NA*
Orthopaedic surgery									
Berenholtz (2009)	Level II *Good*	1 RCT N=182	Adult patients undergoing major spine surgery	Hospital – planned surgery US	E-aminocaproic acid (IV) vs placebo	Reoperation for bleeding	RR 0.20 (0.01, 4.11)[d]	*No difference* 0.30 [d]	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; *het*, heterogeneity; IV, intravenous; NA, not applicable; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Studies conducted in a wide range of countries. Eight of the 211 studies included in the review were conducted in Australia; however, it is unknown how many of these were related specifically to the comparison between.
[d] Post-hoc analysis conducted for this guideline.

Key question(s): In patients undergoing surgery, what is the effect of administration of ε-aminocaproic acid on hospital length of stay?		Evidence table ref[a]: POQ3.I8c.S5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I/II study (Henry 2007/good quality) which contains one RCT (good quality) and one additional RCT (Berenholtz 2009/good quality), both in orthopaedic surgery.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Only one RCT included in Henry review (in orthopaedic surgery) and one additional RCT (in major spine surgery). Results conflicting; both show no significant difference but post estimates in different directions.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Henry 2007 Orthopaedic surgery (days) – MD 2.90 (-0.96, 6.76); 1 RCT (N=46) Supportive evidence – Berenholtz 2009 Major spine surgery (days) – MD -1.00 (-2.94, 0.94); 1 RCT (N=182)	A	Very large
	B	Substantial
	C	Moderate
	D	Inconsistent
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. Both included studies were in orthopaedic surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The location of the single RCT from the Henry review is unknown. The Berenholtz RCT was conducted in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

E-aminocaproic acid is a synthetic derivative of the amino acid lysine. It is not currently TGA-approved for use in Australia.

Generalisability rated C as most evidence in a restricted surgical population but applied to general surgical population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	There is one pivotal Level I/II study (good quality) which contains one RCT (good quality) and one additional RCT, both in orthopaedic surgery.
2. Consistency	D	Conflicting direction of the point estimates between the two RCTs.
3. Clinical impact	D	There was no significant difference in the analyses; however, the results were conflicting.
4. Generalisability	C	The results are generalisable to an adult population undergoing orthopaedic/spine surgery.
5. Applicability	C	One RCT was conducted in the US, the other is unknown. Possibly applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on length of hospital stay, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review;
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8c.S5 Characteristics and results of studies examining the effect of **ε**-aminocaproic acid on hospital length of stay

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV E-AMINOCAPROIC ACID									
Orthopaedic surgery									
Henry (2007)	Level I/II *Good/Good*	1 RCT N=46	Adult patients undergoing orthopaedic surgery	Hospital – planned surgery Unknown	E-aminocaproic acid (IV) vs no ε-aminocaproic acid	Hospital length of stay (days)	MD 2.90 (-0.96, 6.76)	*No difference* 0.14	*NA*
Berenholtz (2009)	Level II *Good*	1 RCT N=182	Adult patients undergoing major spine surgery	Hospital – planned surgery US	E-aminocaproic acid (IV) vs placebo	Hospital length of stay (days)	MD -1.00 (-2.94, 0.94)[c]	*No difference* 0.31[c]	*NA*

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; *het*, heterogeneity; IV, intravenous; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Post-hoc analysis conducted for this Guideline.

Recommendation(s) for administration of ε-aminocaproic acid

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
In adult patients undergoing cardiac surgery, the use of intravenous ε-aminocaproic acid is recommended.	C	PO3.I8c.P1, PO3.I8c.P3

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Increased use of ε-aminocaproic acid.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Drug cost (albeit modest).		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Potential resistance.		
What could help to facilitate implementation of the recommendation?	YES	NO
Education; promotion of PO guideline.		

Intervention 8 – Administration of antifibrinolytics & DDAVP: Desmopressin

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on transfusion incidence?		Evidence table ref[a]: POQ3.I8d.P1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/ fair quality) which includes data from up to 21 RCTs, one supportive Level I study (Carless 2008/ good quality) and one supportive Level I/II study (Gurusamy 2009/good-fair quality) in a specific surgery type (liver resection).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008 No significant heterogeneity (see note) in main analyses and most subgroup analyses. Moderate heterogeneity in analyses of cardiac surgery subgroup. Supportive evidence – Carless 2008 No significant heterogeneity in most analyses except moderate heterogeneity in some subgroups (see attached table).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 Any surgery (all blood products) – 55.1% vs 57.9%; OR 0.88 (0.70, 1.10); 21 RCTs (N=1429) Cardiac surgery (all blood products) – 54.9% vs 57.9%; OR 0.87 (0.68, 1.11); 16 RCTs (N=1213) Cardiac surgery (platelets) – 9.6% vs 9.1%; OR 0.64 (0.41, 1.01); 11 RCTs (N=769) Non-cardiac surgery – 56.6% vs 57.9%; OR 0.93 (0.48, 1.79); 5 RCTs (N=216) Supportive evidence – Carless 2008 (see Summary Table POQ3.I8d.P1) especially surgery type subgroups	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted (primary CABG; complex surgery and non-cardiac surgery; cardiac surgery [platelets only])
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery (16/21 RCTs). There were also analyses of patients undergoing cardiac surgery who had or had not received ASA within 7 days prior to surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied (non-cardiac)
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

The Crescenzi (pivotal) review includes more studies than the Carless (supportive) review due to the more restricted inclusion criteria used in Carless (ie, elective or non-urgent surgery). The Crescenzi review assesses transfusion of whole blood products (including RBCs, FFP and platelets) while the Carless review assesses only transfusion of RBCs. Both the Crescenzi and Carless reviews include any surgery type, while the earlier reviews assessed only cardiac surgery. The Crescenzi review has been rated as *fair* quality due to the lack of formal quality assessment and lack of investigation of heterogeneity. The Carless review assessed quality and performed a subgroup analysis of transfusion incidence for all surgery types based on the rating (A,B or C) of treatment allocation[d]. The analysis showed no substantial difference in the results between studies rated A, B or C, suggesting study quality may not have greatly influenced the findings. All studies included in the Carless review were included in the Crescenzi review. The Carless review performed extensive subgroup analyses for this outcome (shown in Table POQ3.I8d.P1).

There was significant discussion amongst the CRG around different surgical subgroups so separate ratings have been given for each.

EVIDENCE STATEMENT MATRIX

Component	Primary CABG	Complex cardiac	Cardiac (PLT)	Noncardiac	Description
1. Evidence base	A	A	A	A	There is one pivotal Level I study (fair quality), one supportive Level I study and one supportive Level I/II study in a specific surgery type.
2. Consistency	B	B	B	B	Most studies were reasonably consistent. Some heterogeneity in cardiac subgroup analyses
3. Clinical impact	D	D	D	D	There was no significant difference in the majority of surgery types. Large potential risk estimate for platelets in cardiac surgery but not significant, possibly due to underpowering.
4. Generalisability	A	A	A	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	B	B	B	Studies were conducted in a wide range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

In adult patients undergoing primary coronary artery bypass surgery, intravenous desmopressin therapy reduces the incidence of allogeneic blood transfusion compared with no therapy.

In adult patients undergoing complex cardiac surgery, intravenous desmopressin therapy does not reduce the incidence of allogeneic blood transfusion compared with no therapy.

In adult patients undergoing cardiac surgery, intravenous desmopressin therapy may reduce the incidence of platelet transfusion compared with no therapy.

In adult patients undergoing noncardiac surgery in which substantial blood loss is anticipated, intravenous desmopressin therapy does not appear to reduce the incidence of allogeneic blood transfusion compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity if I^2 >50%.
Abbreviations: CI, confidence interval, Pot, potential; RBC, red blood cell; SR, systematic review.
[a] Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission.

OQ3.I8d.P1 Characteristics and results of studies examining the effect of desmopressin on transfusion incidence.

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	21 RCTs N=1429	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Transfusion incidence (blood products)[c]	OR 0.88 (0.70, 1.10)	*No difference* P=0.26	*None* P*het*=0.19 (I^2=21.4%)
Carless (2008)	Level I *Good*	17 RCTs N=1308	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[d]	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.96 (0.87, 1.06)	*No difference* P=0.42	*None* P*het*=0.19 (I^2=22%)
Carless (2008)	Level I *Good*	10 RCTs N=736	Adult patients undergoing any surgery with transfusion protocol	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.90 (0.77, 1.04)	*No difference* P=0.16	*None* P*het*=0.25 (I^2=21%)
		7 RCTs N=572	Adult patients undergoing any surgery without transfusion protocol	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 1.03 (0.93, 1.14)	*No difference* P=0.60	*None* P*het*=0.40 (I^2=4%)
Carless (2008)	Level I *Good*	8 RCTs N=635	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs) using autologous techniques	RR 1.00 (0.84, 1.19)	*No difference* P=0.97	*None* P*het*=0.31 (I^2=15%)
		9 RCTs N=673	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs) not using autologous techniques	RR 0.91 (0.78, 1.07)	*No difference* P=0.25	*Moderate* P*het*=0.04 (I^2=50%)
Carless (2008)	Level I *Good* Rating A[e]	2 RCTs N=190	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.97 (0.75, 1.24)	*No difference* P=0.80	*None* P*het*=0.50 (I^2=0%)
	Level I *Good* Rating B[e]	10 RCTs N=746	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.88 (0.75, 1.03)	*No difference* P=0.12	*Substantial* P*het*=0.04 (I^2=50%)
	Level I *Good* Rating C[e]	5 RCTs N=372	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 1.11 (0.94, 1.33)	*No difference* P=0.22	*None* P*het*=0.75 (I^2=0%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	16 trials N=1213	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Transfusion incidence (blood products)[a]	OR 0.87 (0.68, 1.11)	*No difference* P=0.26	*Moderate* P*het*=0.07 (I^2=37.0%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting Location	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
		11 RCTs N=769	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Transfusion incidence (platelets)	OR 0.64 (0.41, 1.01)	*No difference* P=0.06	*None* Phet=0.22 (I^2=23.1%)
Carless (2008)	Level I *Good*	14 RCTs N=1137	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.95 (0.84, 1.07)	*No difference* P=0.39	*Moderate* P*het*=0.11 (I^2=33%)
Carless (2008)	Level I *Good*	8 RCTs N=527	Adult patients undergoing primary CABG	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.85 (0.73, 0.99)	*Favours DDAVP* P=0.038	*None* P*het*=0.43 (I^2=0%)
		6 RCTs N=610	Adult patients undergoing CABG + valve ± combination/redo surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 1.03 (0.88, 1.19)	*No difference* P=0.75	*Moderate* P*het*=0.14 (I^2=40%)
Carless (2008)	Level I *Good*	5 RCTs N=340	Adult patients undergoing cardiac surgery who have had ASA within 7 days prior	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.89 (0.64, 1.23)	*No difference* P=0.49	*Moderate* P*het*=0.12 (I^2=40%)
		4 RCTs N=286	Adult patients undergoing cardiac surgery who have had no ASA within 7 days prior	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 0.79 (0.62, 1.01)	*No difference* P=0.056	*None* P*het*=0.36 (I^2=7%)
Non-cardiac surgery									
Crescenzi (2008)	Level I *Fair*	5 RCTs N=216	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Transfusion incidence (blood products)[c]	OR 0.93 (0.48, 1.79)	*No difference* P=0.83	*None* Phet=0.81 (I^2=0%)
Carless (2008)	Level I *Good*	3 RCTs N=171	Adults patients undergoing surgery other than cardiac	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (RBCs)	RR 1.01 (0.81, 1.26)	*No difference* P=0.91	*None* P*het*=0.59 (I^2=0%)
Liver surgery									
Gurusamy (2009)	Level I/II *Good/Fair*	1 RCT N=59	Adult patients undergoing liver resection	Hospital – planned surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion incidence (allogenic blood)	RR 0.58 (0.15, 2.21)	*No difference* 0.42	*NA* P*het*=NA (I^2=NA)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CI, confidence interval; FFP, fresh frozen plasma; *het*, heterogeneity; IV, intravenous; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Blood products include RBCs, FFP and platelets.
[d] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.
[e] Cochrane ratings defined as follows: Grade A, adequate allocation concealment; Grade B, uncertain allocation concealment; Grade C, inadequate allocation concealment.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on transfusion volume?		Evidence table ref[a]: POQ3.8d.P2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/fair quality) which includes data from up to 11 RCTs, one supportive Level I study (Carless 2008/good quality) and one supportive level I/II study (Gurusamy 2009/good-fair quality) which includes data from one RCT in liver resection surgery.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008: Substantial heterogeneity (see note) in all analyses. May be due to inclusion of studies measuring transfusion in units and mL. Supportive evidence – Carless 2008: Moderate heterogeneity in analysis including all surgery and all patients. No significant heterogeneity seen in analysis of all surgery including transfused patients only. Moderate to substantial heterogeneity seen in most subgroup analyses which included all patients (ie, those who required transfusion and those who didn't).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 (based on SMD - not easy to interpret differences clinically) Any surgery (all patients) – SMD -0.29 (-0.52, -0.06); 34 RCTs (N=2065) Cardiac surgery (all patients) – SMD -0.22 (-0.52, 0.08); 23 RCTs (N=1607) Non-cardiac surgery (all patients) – SMD -0.45 (-0.77, -0.13); 11 RCTs (N=458) Supportive evidence – Carless 2008 (see Summary Table POQ3.I8d.P2 for all results) Any surgery (all patients) – WMD -0.30 (-0.60, -0.01); 14 RCTs (N=885) Any surgery (transfused patients) – WMD -0.49 (-0.94, -0.04); 5 RCTs (N=211)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were to be included in the overall analysis although the majority of studies were in patients undergoing cardiac surgery (23/34 RCTs). There were also separate analyses of patients undergoing orthopaedic surgery and vascular surgery although these included few studies (2 RCTs each).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

Generalisability rated C as most studies in a specific surgical type but the evidence statement is applied to the general population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (fair quality) and one supportive Level I study and one supportive level I/II study.
2. Consistency	C	There was some heterogeneity, particularly in the pivotal study. May be due to inclusion of different volume measures.
3. Clinical impact	B	There was a significant difference in a number of the main analyses and no difference in others.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a wide range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous desmopressin therapy may reduce the volume of transfusion compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission
[b] Gurusamy included one study only which related to liver resection. This is described where appropriate in the Evidence Statement Summary Tables.
[c] Publication dated 2004 but includes update to March 2008.

POQ3.8d.P2 Characteristics and results of studies examining the effect of desmopressin on transfusion volume

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity*[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	34 RCTs N=2065	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Transfusion volume[c] (blood products) Includes all patients	SMD -0.29 (-0.52, -0.06)	*Favours DDAVP* 0.01	*Substantial* Phet<0.001 (I^2=84.5%)
Carless (2008)	Level I *Good*	14 RCTs N=885	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[d]	Desmopressin (IV) vs no desmopressin	Transfusion volume in units (RBCs) Includes all patients	WMD -0.30 (-0.60, -0.01)	*Favours DDAVP* 0.042	*Moderate* *Phet*=0.07 (I^2=39%)
		5 RCTs N=211	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion volume in units (RBCs) Includes transfused patients only	WMD -0.49 (-0.94, -0.04)	*Favours DDAVP* 0.033	*None* *Phet*=0.49 (I^2=0%)
Carless (2008)	Level I *Good*	4 RCTs N=151	Adult patients undergoing any surgery in whom autologous techniques were used	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion volume in units (RBCs) Includes all patients	WMD -0.47 (-1.15, 0.20)	*No difference* 0.17	*Substantial* *Phet*=0.08 (I^2=56%)
		10 RCTs N=734	Adult patients undergoing any surgery in whom no autologous techniques were used	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion volume in units (RBCs) Includes all patients	WMD -0.22 (-0.55, 0.10)	*No difference* 0.18	*Moderate* *Phet*=0.19 (I^2=28%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	23 trials N=1607	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Transfusion volume (blood products) Includes all patients	SMD -0.22 (-0.52, 0.08)	*No difference* 0.14	*Substantial* *Phet*<0.001 (I^2=87.8%)
Carless (2008)	Level I *Good*	10 RCTs N=621	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion volume in units (RBCs) Includes all patients	WMD -0.39 (-0.77, -0.01)	*Favours DDAVP* 0.047	*Substantial* *Phet*=0.03 (I^2=52%)
Non-cardiac surgery									
Crescenzi (2008)	Level I *Fair*	11 RCTs N=458	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Transfusion volume (blood products) Includes all patients	SMD -0.45 (-0.77, -0.13)	*Favours DDAVP* 0.006	*Substantial* *Phet*=0.003 (I^2=62.4%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		*Heterogeneity[b]*
							Risk estimate (95% CI)	*Significance* P-value	
Orthopaedic surgery									
Carless (2008)	Level I *Good*	2 RCTs N=129	Adults patients undergoing orthopaedic surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion volume in units (RBCs) Includes all patients	WMD -0.15 (-0.64, 0.33)	*No difference* 0.54	*None* P*het*=0.43 (I^2=0%)
Vascular surgery									
Carless (2008)	Level I *Good*	2 RCTs N=135	Adults patients undergoing vascular surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Transfusion volume in units (RBCs) Includes all patients	WMD 0.06 (-0.89, 1.02)	*No difference* 0.90	*None* P*het*=0.40 (I^2=0%)
Liver surgery									
Gurusamy (2009)	Level I/II *Good/Fair*	1 RCT N=59	Adult patients undergoing liver resection	Hospital – planned surgery Unknown	Desmopressin (IV) vs placebo	Transfusion volume in units (RBCs) Includes all patients	SMD -0.31 (-0.82, 0.21)	*No difference* 0.24	*NA* Phet=NA (I2=NA)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; RBC, red blood cell; RCT, randomised controlled trial; SMD, standardised mean difference; WMD , weighted mean difference.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Blood products include RBCs, FFP and platelets. Due to differences in the way this outcome was reported in individual RCTs, the analysis has been performed using the SMD.
[d] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on blood loss?		Evidence table ref[a]: POQ3.8d.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/fair quality) which includes data from up to 11 RCTs, one supportive Level I study (Carless 2008/good quality) and one supportive level I/II study (Gurusamy 2009/good-fair quality) which includes data from one RCT in liver resection surgery.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008 Substantial heterogeneity (see note) in the analysis of all surgery types and cardiac surgery. No heterogeneity in analysis of non-cardiac surgery. Supportive evidence – Carless 2008 (see Summary Table POQ3.I8d.P3) Moderate to substantial heterogeneity seen in most analyses and sub-analyses.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 (based on SMD - not easy to interpret differences clinically) Any surgery – SMD -0.20 (-0.34, -0.06); 40 RCTs (N=2445) Cardiac surgery – SMD -0.23 (-0.40, -0.05); 29 RCTs (N=1928) Non-cardiac surgery – SMD -0.10 (-0.28, 0.07); 11 RCTs (N=517) Supportive evidence – Carless 2008 (see Summary Table POQ3.I8d.P3 for all results) Any surgery – WMD -92.98 (-149.86, -36.11); 18 RCTs (N=1201) Cardiac surgery – WMD -96.58 (-163.04, -30.12); 16 RCTs (N=1107)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery (29/40 RCTs). There were also separate analyses of patients undergoing cardiac surgery who did or did not receive ASA.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

In cardiac surgery, the difference was statistically significant but not clinically important.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Cardiac	Description
1. Evidence base	A	There is one pivotal Level I study (fair quality) and one supportive Level I study and one supportive level I/II study.
2. Consistency	C	There was some heterogeneity, particularly in the pivotal study. May be due to different surgery types and blood loss measures used in different studies.
3. Clinical impact	D	There was a significant difference in most of the main analyses and no difference in some subgroup analyses
4. Generalisability	B	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a wide range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, intravenous desmopressin therapy reduces blood loss compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.8d.P3 Characteristics and results of studies examining the effect of desmopressin on blood loss

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IC DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	40 RCTs N=2445	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Blood loss (mL)	SMD -0.20 (-0.34, -0.06)	*Favours DDAVP* 0.004	*Substantial* P*het*<0.001 (I^2=63.7%)
Carless (2008)	Level I *Good*	7 RCTs N=493	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[c]	Desmopressin (IV) vs no desmopressin	Intraoperative blood loss (mL)	WMD -90.07 (-199.56, 19.42)	*No difference* 0.11	*Moderate* P*het*=0.17 (I^2=34%)
		12 RCTs N=787	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	0-24 hours postoperative blood loss (mL)	WMD –100.41 (-176.48, -24.34)	*Favours DDAVP* 0.0097	*Substantial* P*het*=0.004 (I^2=59%)
		18 RCTs N=1201	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss (mL)	WMD -92.98 (-149.86, -36.11)	*Favours DDAVP* 0.0014	*Substantial* P*het*=0.001 (I^2=58%)
		10 RCTs N=669	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Intraoperative + postoperative blood loss(mL)	WMD -241.78 (-387.55, -96.01)	*Favours DDAVP* 0.0012	*Substantial* P*het*=0.002 (I^2=66%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	29 trials N=1928	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Blood loss (mL)	SMD -0.23 (-0.40, -0.05)	*Favours DDAVP* 0.01	*Substantial* P*het*<0.001 (I^2=71.0%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
Carless (2008)	Level I *Good*	3 RCTs N=229	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Intraoperative blood loss (mL)	WMD -119.79 (-314.57, 75.00)	*No difference* 0.23	*Substantial* P*het*=0.06 (I^2=65%)
		1 RCT N=59	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	0-6 hours postoperative blood loss (mL)	WMD -98.00 (-304.99, 108.99)	*No difference* 0.35	*NA* P*het*=NA (I^2=NA)
		3 RCTs N=233	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	0-12 hours postoperative blood loss (mL)	WMD -114.05 (-269.46, 41.36)	*No difference* 0.15	*Substantial* P*het*=0.004 (I^2=82%)
		2 RCTs N=122	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	0-16 hours postoperative blood loss (mL)	WMD –18.01 (-113.34, 77.32)	*No difference* 0.71	*None* P*het*=0.42 (I^2=0%)
		10 RCTs N=693	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	0-24 hours postoperative blood loss (mL)	WMD –107.46 (-207.12, -7.80)	*Favours DDAVP* 0.035	*Substantial* P*het*=0.002 (I^2=65%)
		16 RCTs N=1107	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss (mL)	WMD -96.58 (-163.04, -30.12)	*Favours DDAVP* 0.0044	*Substantial* P*het*<0.001 (I^2=62%)
		7 RCTs N=496	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Intraoperative + postoperative blood loss (mL)	WMD -237.92 (-413.43, -62.40)	*Favours DDAVP* 0.0079	*Substantial* P*het*<0.001 (I^2=74%)
Carless (2008)	Level I *Good*	10 RCTs N=633	Adult patients undergoing cardiac surgery with ASA use	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss (mL)	WMD -109.57 (-200.11, -19.03)	*Favours DDAVP* 0.018	*Substantial* P*het*=0.01 (I^2=60%)
		3 RCTs N=221	Adult patients undergoing cardiac surgery without ASA use	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss (mL)	WMD -112.69 (-227.59, 2.22)	*No difference* 0.055	*Moderate* P*het*=0.16 (I^2=45%)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
Carless (2008)	Level I *Good*	3 RCTs N=198	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss after CPB < 80 mins (mL)	WMD -41.22 (-157.25, 74.80)	*No difference* 0.49	*Substantial* Phet=0.07 (I^2=62%)
		5 RCTs N=330	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss after CPB 80 – 100 mins (mL)	WMD -104.18 (-184.75, -23.61)	*Favours DDAVP* 0.011	*Moderate Phet=0.21 (I^2=31%)*
		3 RCTs N=129	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss after CPB 101 – 120 mins (mL)	WMD 53.08 (-156.33, 262.50)	*No difference* 0.62	*Moderate Phet=0.15 (I^2=47%)*
		2 RCTs N=196	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss after CPB 121 – 140 mins (mL)	WMD -46.53 (-366.29, 273.23)	*No difference* 0.78	*Substantial Phet=0.01 (I^2=84%)*
		2 RCTs N=171	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss after CPB > 140 mins (mL)	WMD -344.74 (-478.50, -210.97)	*Favours DDAVP* <0.001	*None Phet=0.42 (I^2=0%)*
		15 RCTs N=1024	Adult patients undergoing cardiac surgery	Hospital – elective or non-urgent surgery Various	Desmopressin (IV) vs no desmopressin	Postoperative blood loss after CPB of any duration (mL)	WMD -93.34 (-162.24, -24.44)	*Favours DDAVP* 0.0079	*Substantial Phet<0.001 (I^2=64%)*
Non-cardiac surgery									
Crescenzi (2008)	Level I *Fair*	11 RCTs N=517	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Blood loss (mL)	SMD -0.10 (-0.28, 0.07)	*No difference* 0.25	*None* Phet=0.45 (I^2=0%)
Liver surgery									
Gurusamy (2009)	Level I/II *Good/Fair*	1 RCT N=97	Adult patients undergoing liver resection	Hospital – planned surgery Various	Desmopressin (IV) vs no desmopressin	Operative blood loss (mL)	MD 32.50 (-695.69, 760.69)	*No difference* 0.93	*NA* Phet=NA (I^2=NA)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.

Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; CPB, cardiopulmonary bypass; MD, mean difference; NA, not applicable; RBC, red blood cell; RCT, randomised controlled trial; SMD, standardised mean difference; WMD , weighted mean difference.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on mortality?		Evidence table ref[a]: POQ3.I8d.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/fair quality) which includes data from up to 8 RCTs and one supportive Level I study (Carless 2008/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008 No heterogeneity in analyses of any surgery or cardiac surgery (non-cardiac surgery analysis includes data from only 1 RCT) Supportive evidence – Carless 2008 No heterogeneity in analyses of any surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 Any surgery – 1.2% vs 0.9%; OR 1.25 (0.51, 3.04); 8 RCTs (N=673) Cardiac surgery – 1.0% vs 1.1%; OR 1.00 (0.38, 2.62); 7 RCTs (N=582) Non-cardiac surgery – 2.1% vs 0%; OR 5.84 (0.27, 125.19); 1 RCT (N=91) Supportive evidence – Carless 2008 Any surgery – 2.4% vs 1.3%; RR 1.72 (0.68, 4.33); 8 RCTs (N=774)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery (7/8 RCTs). There were also separate analyses of patients undergoing cardiac surgery or non-cardiac surgery. However, the non-cardiac surgery analysis includes data from only one RCT in vascular surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

Generalisability rated C as most studies in a specific surgical type but the evidence statement is applied to the general population.

The CRG noted that the point estimate indicated a potentially increased risk of mortality, although the evidence is underpowered to show a difference (difference not statistically significant).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (fair quality) and one supportive Level I study.
2. Consistency	A	There was no heterogeneity between studies
3. Clinical impact	D	There was no significant difference in all analyses. The studies are likely underpowered to detect a difference in mortality.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on mortality, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
Abbreviations: CI, confidence interval, Pot, potential; RBC, red blood cell; SR, systematic review.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.8d.P4 Characteristics and results of studies examining the effect of desmopressin on mortality

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	8 RCTs N=673	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Mortality	OR 1.25 (0.51, 3.04)	*No difference* 0.63	*None* P*het*=0.76 (I^2=0%)
Carless (2008)	Level I *Good*	8 RCTs N=774	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[c]	Desmopressin (IV) vs no desmopressin	Mortality	RR 1.72 (0.68, 4.33)	*No difference* 0.25	*None* P*het*=0.80 (I^2=0%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	7 trials N=582	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Mortality	OR 1.00 (0.38, 2.62)	*No difference* 1.00	*None* P*het*=0.81 (I^2=0%)
Non-cardiac surgery									
Crescenzi (2008)	Level I/II *Fair/ Unknown*	1 RCT N=91	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Mortality	OR 5.84 (0.27, 125.19)	*No difference* 0.26	*NA* P*het*=NA (I^2=NA)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on morbidity (hypotension)?		Evidence table ref[a]: POQ3.I8d.P5 (hypotension)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/fair quality) including data from up to 13 RCTs and one supportive Level I study (Carless 2008/good quality).	A	One or more level I studies with a low rik of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008 No heterogeneity in analyses of any surgery, cardiac surgery or non-cardiac surgery Supportive evidence – Carless 2008 No heterogeneity in analyses of any surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 Any surgery – 8.2% vs 2.1%; OR 4.84 (2.31, 10.13); 7 RCTs (N=320) Cardiac surgery – 5.2% vs 0.3%; OR 8.92 (2.54, 31.37); 5 RCTs (N=221) Non-cardiac surgery – 22.0% vs 9.6%; OR 3.04 (1.18, 7.87); 2 RCTs (N=99) Supportive evidence – Carless 2008 Any surgery – 37.0% vs 9.9%; RR 2.81 (1.50, 5.27); 5 RCTs (N=183)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery (5/7 RCTs). There were also separate analyses of patients undergoing cardiac surgery or non-cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

Generalisability rated C as most studies in a specific surgical type but the evidence statement is applied to the general population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (fair quality) and one supportive Level I study.
2. Consistency	A	There was no heterogeneity in the Level I studies and the two Level I studies showed consistent results.
3. Clinical impact	D	There was a significant risk of hypotension for desmopressin therapy compared with no therapy but the authors note that this is transient and mild.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous desmopressin therapy increases the risk of mild and transient hypotension compared with no therapy.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
Abbreviations: CI, confidence interval, RBC, red blood cell; SR, systematic review.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8d.P5 (hypotension) Characteristics and results of studies examining the effect of desmopressin on morbidity (hypotension)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	Significance P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	7 RCTs N=320	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Hypotension	OR 4.84 (2.31, 10.13)	*Favours no desmopressin* <0.001	*None* P*het*=0.85 (I^2=0%)
Carless (2008)	Level I *Good*	5 RCTs N=183	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[c]	Desmopressin (IV) vs no desmopressin	Hypotension during infusion requiring treatment (fluids and/or vasoactive drugs)	RR 2.81 (1.50, 5.27)	*Favours no desmopressin* 0.0013	*None* P*het*=0.50 (I^2=0%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	5 RCTs N=221	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Hypotension	OR 8.92 (2.54, 31.37)	*Favours no desmopressin* <0.001	*None* P*het*=0.94 (I^2=0%)
Non-cardiac surgery									
Crescenzi (2008)	Level I *Fair*	2 RCTs N=99	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Hypotension	OR 3.04 (1.18, 7.87)	*Favours no desmopressin* 0.02	*None* P*het*=0.64 (I^2=0%)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on morbidity (myocardial infarction)?		Evidence table ref[a]: POQ3.I8d.P5 (MI)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/fair quality) which includes data from up to 13 RCTs and one supportive Level I study (Carless 2008/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008 No heterogeneity in analyses of any surgery, cardiac surgery or non-cardiac surgery. Difference in direction of effect for different surgery types. Supportive evidence – Carless 2008 No heterogeneity in analyses of any surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 Any surgery – 3.8% vs 2.9%; OR 1.27 (0.73, 2.20); 13RCTs (N=916) Cardiac surgery – 4.3% vs 3.1%; OR 1.36 (0.75, 2.48); 11 RCTs (N=775) Non-cardiac surgery – 1.8% vs 2.2%; OR 0.84 (0.20,3.53); 2 RCTs (N=141) Supportive evidence – Carless 2008 Any surgery – 6.3% vs 4.1%; RR 1.38 (0.77, 2.50); 9 RCTs (N=731)	A	Very large
	B	Substantial
	C	Moderate
	D	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery (11/13 RCTs). There were also separate analyses of patients undergoing cardiac surgery or non-cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

Generalisability rated C as most studies in a specific surgical type but the evidence statement is applied to the general population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (fair quality) and one supportive Level I study.
2. Consistency	B	There was no heterogeneity in the two included Level I studies. There was a difference in the direction of effect for cardiac surgery versus non-cardiac surgery.
3. Clinical impact	D	Results show an slightly increased risk with no significant difference (28/441 versus 19/435 in any surgery) but studies likely underpowered to detect a difference in myocardial infarction.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on risk of myocardial infarction, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8d.P5 (MI) Characteristics and results of studies examining the effect of desmopressin on morbidity (myocardial infarction)

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	13 RCTs N=916	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Myocardial infarction	OR 1.27 (0.73, 2.20)	*No difference* 0.40	*None* P*het*=0.88 (I^2=0%)
Carless (2008)	Level I *Good*	9 RCTs N=731	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[c]	Desmopressin (IV) vs no desmopressin	Myocardial infarction	RR 1.38 (0.77, 2.50)	*No difference* 0.28	*None* P*het*=0.87 (I^2=0%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	11 RCTs N=775	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Myocardial infarction	OR 1.36 (0.75, 2.48)	*No difference* 0.31	*None* P*het*=0.86 (I^2=0%)
Non-cardiac surgery									
Crescenzi (2008)	Level I *Fair*	2 RCTs N=141	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Myocardial infarction	OR 0.84 (0.20,3.53)	*No difference* 0.81	*None* P*het*=0.35 (I^2=0%)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on morbidity (stroke)?		Evidence table ref[a]: POQ3.I8d.P5 (stroke)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one supportive Level I study (Carless 2008/good quality) which includes data from seven RCTs.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Supportive evidence – Carless 2008 No heterogeneity in analyses of any surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Supportive evidence – Carless 2008 Any surgery – 4.3% vs 1.1%; RR 2.40 (0.68, 8.43); 7 RCTs (N=591)	A	Very large
	B	Substantial (potential)
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The Carless 2008 study states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

Generalisability rated C as most studies in a specific surgical type but the evidence statement is applied to the general population.

The CRG noted that the point estimate indicated a potentially increased risk of stroke, although the evidence is underpowered to show a difference (difference not statistically significant).

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one supportive Level I study (good quality) which includes data from seven RCTs.
2. Consistency	A	There was no heterogeneity between studies
3. Clinical impact	D	There was no significant difference in the analysis. The studies are likely underpowered to detect a difference in risk of stroke.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on risk of stroke, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
Abbreviations: CI, confidence interval, Pot, potential; SR, systematic review.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8d.P5 (stroke) Characteristics and results of studies examining the effect of desmopressin on morbidity (stroke)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Carless (2008)	Level I *Good*	7 RCTs N=591	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[c]	Desmopressin (IV) vs no desmopressin	Stroke	RR 2.40 (0.68, 8.43)	*No difference* 0.17	*None* *Phet*=0.90 (I^2=0%)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on morbidity (thrombosis)?		Evidence table ref[a]: POQ3.I8d.P5 (thrombosis)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/fair quality) which includes data from up to 14 RCTs and one supportive Level I study (Carless 2008/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008 No heterogeneity in analyses of any surgery or cardiac surgery. Moderate heterogeneity in analysis of non-cardiac surgery (3 RCTs only) Supportive evidence – Carless 2008 No heterogeneity in analyses of any surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 Any surgery – 2.9% vs 2.5%; OR 1.20 (0.68, 2.09); 14 RCTs (N=1151) Cardiac surgery – 2.5% vs 2.0%; OR 1.27 (0.64, 2.50); 11 RCTs (N=931) Non-cardiac surgery – 4.4% vs 4.1%; OR 1.06 (0.39,2.84); 3 RCTs (N=220) Supportive evidence – Carless 2008 Any surgery – 3.9% vs 3.0%; RR 1.46 (0.64, 3.35); 7 RCTs (N=591)	A	Very large
	B	Substantial
	C	Moderate (potential)
	D	Slight/restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery (11/14 RCTs). There were also separate analyses of patients undergoing cardiac surgery or non-cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

Generalisability rated C as most studies in a specific surgical type but the evidence statement is applied to the general population.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (fair quality) and one supportive Level I study.
2. Consistency	A	There was no heterogeneity in the Level I studies and consistent results between the two studies.
3. Clinical impact	D	Results show a slightly increased risk with no significant difference (14/361 versus 10/330 in any surgery) but studies likely underpowered to detect a difference in thrombosis.
4. Generalisability	C	The results are generalisable to an adult surgical population; in particular those undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on risk of thrombosis, compared with no therapy, is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
Abbreviations: CI, confidence interval, SR, systematic review.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8d.P5 (thrombosis) Characteristics and results of studies examining the effect of desmopressin on morbidity (thrombosis)

Study	Level of evidence[a] *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	14 RCTs N=1151	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Thromboses (other than myocardial infarction)	OR 1.20 (0.68, 2.09)	*No difference* 0.53	*None* P*het*=0.82 (I^2=0%)
Carless (2008)	Level I *Good*	7 RCTs N=591	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[c]	Desmopressin (IV) vs no desmopressin	Any thrombosis	RR 1.46 (0.64, 3.35)	*No difference* 0.37	*None* P*het*=0.78 (I^2=0%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	11 RCTs N=931	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Thromboses (other than myocardial infarction)	OR 1.27 (0.64, 2.50)	*No difference* 0.49	*None* P*het*=0.86 (I^2=0%)
Non-cardiac surgery									
Crescenzi (2008)	Level I *Fair*	3 RCTs N=220	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Thromboses (other than myocardial infarction)	OR 1.06 (0.39,2.84)	*No difference* 0.92	*Moderate* P*het*=0.24 (I^2=30.2%)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on quality of life?		Evidence table ref[a]: POQ3.I8d.P6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies of any level were identified which assessed the effect of desmopressin on quality of life. .	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of desmopressin therapy on quality of life, compared with no therapy, is unknown.

Abbreviations: NA, not applicable.

[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of administration of desmopressin on reoperation for bleeding?		Evidence table ref[a]: POQ3.I8d.S2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one pivotal Level I study (Crescenzi 2008/fair quality) including data from up to 15 RCTs, and one supportive Level I study (Carless 2008/good quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Results consistent between pivotal and supportive meta-analyses. Consistency of individual studies within meta-analyses described below. Pivotal evidence – Crescenzi 2008 No heterogeneity in analyses of any surgery, cardiac surgery or non-cardiac surgery Supportive evidence – Carless 2008 No heterogeneity in analyses of any surgery.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pivotal evidence – Crescenzi 2008 Any surgery – 2.8% vs 4.4%; OR 0.65 (0.39, 1.09); 15 RCTs (N=1186) Cardiac surgery – 2.8% vs 4.7%; OR 0.63 (0.36, 1.08); 14 RCTs (N=1136) Non-cardiac surgery – 2.6% vs 2.5%; OR 1.00 (0.18,5.51); 1 RCT (N=50) Supportive evidence – Carless 2008 Any surgery – 1.8% vs 3.5%; RR 0.69 (0.26, 1.83); 9 RCTs (N=693)	A	Very large
	B	Substantial (potential)
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing planned surgery. All surgery types were included in the overall analysis although studies were predominantly in cardiac surgery (14/15 RCTs). There were also separate analyses of patients undergoing cardiac surgery or non-cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Hospital setting. The pivotal review does not state which countries the RCTs were conducted in but the supportive study (which includes most of the studies included in the pivotal review) states that studies were conducted in US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Desmopressin injection currently listed by TGA for the following indication: "patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure".

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	A	There is one pivotal Level I study (fair quality) and one supportive Level I study.
2. Consistency	A	There was no heterogeneity in the Level I studies and consistent results between the two studies.
3. Clinical impact	B	There was no significant difference in all analyses; however, there was a slight trend towards favouring DDAVP in cardiac surgery. The included studies may not be suffiently powered to detect a difference.
4. Generalisability	A	The results are generalisable to an adult surgical population undergoing cardiac surgery
5. Applicability	B	Studies were conducted in a range of countries. Likely to be applicable to the Australian setting

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing cardiac surgery, the effect of intravenous desmopressin therapy on risk of reoperation due to bleeding compared with no therapy is uncertain.

Note: Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if Phet<0.1 and I^2 <25%; moderate heterogeneity if P>0.1 and I^2 between 25-50%; substantial heterogeneity if P<0.1 and I^2 >50%.
Abbreviations: CI, confidence interval, Pot, potential; RBC, red blood cell; SR, systematic review.
[a] Interventions: 1 = ANH, 2 = intraoperative cell salvage, 3 = perioperative ANH and intraoperative cell salvage, 4 = postoperative cell salvage, 5 = deliberate induced hypotension, 6 = prevention of hypothermia, 7 = point-of-care testing for coagulation status and haemoglobin, 8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, 9 = appropriate patient positioning, 10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I8d.S2 Characteristics and results of studies examining the effect of desmopressin on reoperation for bleeding

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results		Heterogeneity[b]
							Risk estimate (95% CI)	*Significance* P-value	
ADULT POPULATION/IV DESMOPRESSIN									
Any surgery									
Crescenzi (2008)	Level I *Fair*	15 RCTs N=1186	Adult patients undergoing any surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Surgical revision for bleeding	OR 0.65 (0.39, 1.09)	*No difference* 0.11	*None* P*het*=0.50 (I^2=0%)
Carless (2008)	Level I *Good*	9 RCTs N=693	Adult patients undergoing any surgery	Hospital – elective or non-urgent surgery Various[c]	Desmopressin (IV) vs no desmopressin	Reoperation for bleeding	RR 0.69 (0.26, 1.83)	*No difference* 0.45	*None* P*het*=0.39 (I^2=6%)
Cardiac surgery									
Crescenzi (2008)	Level I *Fair*	14 RCTs N=1136	Adult patients undergoing cardiac surgery	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Surgical revision for bleeding	OR 0.63 (0.36, 1.08)	*No difference* 0.09	*None* P*het*=0.44 (I^2=0.6%)
Non-cardiac surgery									
Crescenzi (2008)	Level I/II *Fair/ Unknown*	1 RCT N=50	Adults patients undergoing surgery other than cardiac	Hospital – any surgery Countries not specified	Desmopressin (IV) vs placebo	Surgical revision for bleeding	OR 1.00 (0.18,5.51)	*No difference* 1.00	*NA* P*het*=NA (I^2=NA)

Note: Studies providing pivotal evidence for the Evidence Statement Form are shown in shading. Unshaded studies provide supportive evidence.
Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland, UK.

Recommendation(s) for administration of desmopressin

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
No recommendation made due to safety concerns.		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?	YES	NO

Intervention 9 – Appropriate patient positioning

Key question(s): In patients undergoing surgery, what is the effect of patient positioning on transfusion incidence?			Evidence table ref*: POQ3.I9.P1
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Four level II studies: Park 2000 (N=40); good quality. Pace et al. 2008 (N=101), Ong et al. 2003 (N=60), Widman et al. 2001 (N=74); all fair quality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
None of the studies observed a significant effect of alternate patient positioning on the incidence of transfusion during surgery. Two studies examined the use of the lateral position compared to supine position during hip arthroplasty. However, both studies failed to detect a significant effect of patient positioning on transfusion incidence.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
There were no significant effects observed in any of the studies. The examination of different surgical procedures and the use of different patient positions in each study makes it difficult to assess the clinical impact of the patient positions examined.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	No difference	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The four studies identified examined patients undergoing hip arthroplasty, knee surgery and lumbar spinal surgery. As such the evidence is likely generalisable to patients undergoing such surgical procedures.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
There were two studies conducted in the UK and one in Sweden. The evidence from these studies are likely applicable in the Australian context. The fourth study, examining lumbar spinal surgery, was conducted in South Korea. Differences in the healthcare system between South Korea and Australia may limit the applicability of the evidence in the Australian context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	1 good quality RCT and 3 fair quality RCT.
2. Consistency	B	All four studies examined patients undergoing orthopaedic surgery. None of the studies observed a significant effect of patient positioning on transfusion incidence.
3. Clinical impact	D	No significant effect was observed
4. Generalisability	B	The four studies identified examined patients undergoing hip arthroplasty, knee surgery and lumbar spinal surgery. As such the evidence is likely generalisable to patients undergoing such surgical procedures.
5. Applicability	B	There were two studies conducted in the UK and one in Sweden. The evidence from these studies are likely applicable in the Australian context. One study was conducted in South Korea, differences in their healthcare system may limit the applicability of the evidence in the Australian context.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing orthopaedic surgery, the effect of patient positioning on the incidence of allogeneic blood transfusion is uncertain.

POQ3.I9.P1 Characteristics and results of studies examining the effect of patient positioning on transfusion incidence

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention / Comparator	Outcome	Results				Notes
							Intervention		Comparator	p-value	
Pace et al. (2008)	Level II *Fair*	N=101	Patients undergoing hip arthroplasty.	Hospital in UK.	Lateral position / Supine position	Transfusion incidence n/N (%)	5/51 (9.8)		8/50 (16)	P=0.65	–
Ong et al. (2003)	Level II *Fair*	N=60	Patients undergoing primary unilateral total knee replacement for osteoarthritis.	Hospital in UK.	Intervention A: Leg elevated with knee flexed Intervention B: Leg elevated with knee extended Comparator: Knee extended and level with bed	Transfusion incidence n/N (%)	Intervention A	Intervention B	11/20 (55)	P=0.3	–
							7/20 (35)	7/20 (35)			
Widman et al. (2001)	Level II *Fair*	N=74	Patients undergoing hip replacement surgery.	Hospital in Sweden	Lateral position / Supine position	Transfusion incidence n/N (%)	17/30 (57)		30/44 (68)	P=0.336	–
Park 2000	Level II *Good*	N=40	ASA class I and II patients undergoing posterior lumbar spinal surgery.	Hospital in South Korea.	Narrow pad width on support / Wide pad width on spinal support	Transfusion incidence n/N (%)	5/20 (25)		1/20 (5)	NS	–

Abbreviations: ASA, American Society of Anaesthesiologists; NS, not statistically significant.

Key question(s): In patients undergoing surgery, what is the effect of patient positioning on transfusion volume?			Evidence table ref*: POQ3.I9.P2
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Three level II studies: Park 2000 (N=40); good quality. Ong et al. 2003 (N=60), Widman et al. 2001 (N=74); both fair quality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
None of the studies observed a significant effect of alternate patient positioning on the incidence of transfusion during surgery.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
There were no significant effects observed in any of the studies. The examination of different surgical procedures and the use of different patient positions in each study make it difficult to assess the clinical impact of the patient positions examined.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	No difference	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The three studies identified examined patients undergoing hip arthroplasty, knee surgery and lumbar spinal surgery. As such the evidence is likely generalisable to patients undergoing such surgical procedures.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
One study was conducted in the UK and one in Sweden. The evidence from these studies are likely applicable in the Australian context. The third study, examining lumbar spinal surgery, was conducted in South Korea. Differences in the healthcare system between South Korea and Australia may limit the applicability of the evidence in the Australian context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	1 good quality RCT and 2 fair quality RCT.
2. Consistency	A	None of the studies observed a significant effect.
3. Clinical impact	D	No significant effect was observed
4. Generalisability	B	The three studies identified examined patients undergoing hip arthroplasty, knee surgery and lumbar spinal surgery. As such the evidence is likely generalisable to patients undergoing such surgical procedures.
5. Applicability	C	One study was conducted in the UK and one in Sweden. The evidence from these studies are likely applicable in the Australian context. One study was conducted in South Korea; differences in their healthcare system may limit the applicability of the evidence in the Australian context.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing orthopaedic surgery, the effect of patient positioning on the volume of allogeneic blood transfusion is uncertain.

POQ3.I9.P2 Characteristics and results of studies examining the effect of patient positioning on transfusion volume

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention / Comparator	Outcome	Results				Notes
							Intervention		Comparator	p-value	
Ong et al. (2003)	Level II *Fair*	N=60	Patients undergoing primary unilateral total knee replacement for osteoarthritis.	Hospital in UK	Intervention A: Leg elevated with knee flexed Intervention B: Leg elevated with knee extended Comparator: Knee extended and level with bed	Blood transfusion dose Median (range)	Intervention A 0 (0, 2)	Intervention B 0 (0, 2)	2 (0, 3.5)	P=0.3	–
Widman et al. (2001)	Level II *Fair*	N=74	Patients undergoing hip replacement surgery.	Hospital in Sweden	Lateral position / Supine position	Blood transfusion dose Mean (SD)	321mL (341)		407mL (362)	P=0.307	–
Park 2000	Level II *Good*	N=40	ASA class I and II patients undergoing posterior lumbar spinal surgery.	Hospital in South Korea	Narrow pad width on support / Wide pad width on spinal support	Blood transfusion dose Mean (SD)	2.2 Units (NR)		2 Units (NR)	NS	–

Abbreviations: ASA, American Society of Anaesthesiologists; NR, not reported; NS, not statistically significant; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of patient positioning on blood loss?		Evidence table ref*: POQ3.I9.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Five level II studies: Park 2000 (N=40); good quality. Ko et al. 2008 (N=60), Pace et al. 2008 (N=101), Widman et al. 2001 (N=74); all fair quality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Patient positioning had a significant effect on blood loss in four out of the five studies. Two studies examined the effect of lateral versus supine position during hip arthroplasty, however, a significant effect was only observed in one of the studies.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The effect of patient position on the volume of blood loss was 442mL during spinal surgery, 125.7mL during endoscopic sinus surgery, and between 27mL to 215mL during hip arthroplasty, The examination of different surgical procedures and the use of different patient positions in each study make it difficult to synthesise a single effect estimate for the clinical impact of the patient positioning.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The five studies identified examined patients undergoing endoscopic sinus surgery, hip arthroplasty and lumbar spinal surgery. As such the evidence is likely generalisable to patients undergoing such surgical procedures.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Three of the studies were conducted in the UK and Sweden. The evidence from these studies are likely applicable in the Australian context. One study was conducted in South Korea, while another was conducted in Taiwan. Differences in the healthcare system of these countries with Australia may limit the applicability of the evidence in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The study by Ko et al. examined blood loss during endoscopic sinus surgery. In this study, the importance of blood loss is related more to the obstruction of surgical field rather than to issues relating to blood transfusion requirements. Consequently, less emphasis has been placed on the findings from this study.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	1 good quality RCT and 3 fair quality RCT.
2. Consistency	C	3 of the 4 studies found a significant effect of patient positioning on blood loss.
3. Clinical impact	D	The effect of patient position on the volume of blood loss varied between 27mL to 442mL.
4. Generalisability	B	The five studies identified examined patients undergoing endoscopic sinus surgery, hip arthroplasty and lumbar spinal surgery. As such the evidence is likely generalisable to patients undergoing such surgical procedures.
5. Applicability	B	Two studies were conducted in the UK and Sweden. The evidence from these studies are likely applicable in the Australian context. One study was conducted in South Korea, while another was conducted in Taiwan. Differences in the healthcare system of these countries with Australia may limit the applicability of the evidence in the Australian context.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing certain types of surgery, the head-up and lateral patient positions are associated with reduced blood loss.

POQ3.I9.P3 Characteristics and results of studies examining the effect of patient positioning on blood loss

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention / Comparator	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Ko et al. (2008)	Level II *Fair*	N=60	Patients undergoing Endoscopic sinus surgery.	Hospital in Taiwan.	Reverse Trendelenburg position / Supine position	Blood loss (mL) Mean (SD)	126.0 (85.8)	251.7 (139.1)	P<0.001	Difference in blood loss: 125.7mL
Pace et al. (2008)	Level II *Fair*	N=101	Patients undergoing hip arthroplasty.	Hospital in UK.	Lateral position / Supine position	Blood loss (mL) Mean (95% CI)	1129 (989, 1310)	1156 (954, 1265)	P=0.41	Difference in blood loss: 27mL
Widman et al. (2001)	Level II *Fair*	N=74	Patients undergoing hip replacement surgery.	Hospital in Sweden	Lateral position / Supine position	Blood loss (mL) Mean (SD)	Intraoperative: 508 (316)	723 (316)	P=0.001	Difference in blood loss: 215mL
							After 24 hr: 1273 (407)	1374 (458)	P=0.043	Difference in blood loss: 101mL
Park 2000	Level II *Good*	N=40	ASA class I and II patients undergoing posterior lumbar spinal surgery.	Hospital in South Korea.	Narrow pad width on support / Wide pad width on spinal support	Blood loss (mL) Mean (SD)	878 (521)	436 (159)	P<0.05	Difference in blood loss: 442mL

Abbreviations: ASA, American Society of Anaesthesiologists; CI, confidence interval; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of patient positioning on mortality?		Evidence table ref*: POQ3.I9.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There were no level I or II studies that reported data on mortality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	There were no level I or II studies that reported data on mortality.
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of patient positioning on mortality is unknown.

Key question(s): In patients undergoing surgery, what is the effect of patient positioning on morbidity?		Evidence table ref*: POQ3.I9.P5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Three level II studies: DeSio et al. 2008 (N=75); good quality. Pace et al. 2008 (N=101), Ong et al. 2003 (N=60); both fair quality	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
None of the studies observed a significant effect of patient positioning on morbidity outcomes Two studies examined the effect of patient positioning on the incidence of DVT; none of the studies observed a significant effect.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There were no significant effects observed in any of the studies. The examination of different surgical procedures and the use of different patient positions in each study make it difficult to assess the clinical impact of the patient positions examined.	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The three studies identified examined patients undergoing nephrolithotomy, hip arthroplasty and knee surgery. As such the evidence is likely generalisable to patients undergoing these surgical procedures.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in the UK or Italy, as such the evidence from these studies are likely applicable in the Australian context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	1 good quality RCT and 2 fair quality RCT.
2. Consistency	A	None of the studies observed a significant effect of patient positioning on morbidity outcomes
3. Clinical impact	D	There were no significant effects observed in any of the studies.
4. Generalisability	B	The three studies identified examined patients undergoing nephrolithotomy, hip arthroplasty and knee surgery. As such the evidence is likely generalisable to patients undergoing these surgical procedures.
5. Applicability	B	The studies were conducted in the UK or Italy, as such the evidence from these studies are likely applicable in the Australian context.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of patient positioning on morbidity is uncertain.

POQ3.I9.P5 Characteristics and results of studies examining the effect of patient positioning on morbidity

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention / Comparator	Outcome	Results				Notes
							Intervention		Comparator	p-value	
DeSio et al. (2008)	Level II *Good*	N=75	Patients undergoing nephrolithotomy.	Medical institutions in Italy.	Modified supine position / Prone position	Major complications [a] n/N (%)	1/39 (2.6)		0/36 (0)	P=0.2	–
						Minor complications [b] n/N (%)	7/39 (18)		5/36 (14)	P=0.16	–
Pace et al. (2008)	Level II *Fair*	N=101	Patients undergoing hip arthroplasty.	Hospital in UK.	Lateral position / Supine position	Incidence of DVT n/N (%)	1/51 (1.9)		0/50 (0)	NS	–
						Wound infection n/N (%)	0/51 (0)		2/50 (4)	NS	–
Ong et al. (2003)	Level II *Fair*	N=60	Patients undergoing primary unilateral total knee replacement for osteoarthritis.	Hospital in UK.	Intervention A: Leg elevated with knee flexed Intervention B: Leg elevated with knee extended Comparator: Knee extended and level with bed	Incidence of DVT n/N (%)	Intervention A	Intervention B	0/20 (0)	NR	–
							1/20 (5)	1/20 (5)			
						Knee sweeling (cm) Mean (range)	Intervention A	Intervention B	3.8 (1.5, 8.0)	P=0.6	–
							3.4 (1.0, 7.0)	3.3 (1.5, 8.0)			

Abbreviations: DVT, deep vein thrombosis; NR, not reported; NS, not significant; SD, standard deviation.

[a] Major complications include septicaemia, haemorrhaging requiring transfusion, thoracic or abdominal organ injury, acute pancreatitis.

[b] Minor complications include fever, insignificant bleeding, urinary tract infection, colic.

Key question(s): In patients undergoing surgery, what is the effect of patient positioning on quality of life?		Evidence table ref*: POQ3.I9.P6
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There were no studies that reported data on quality of life.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
NA	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
NA	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
NA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	There were no studies that reported data on quality of life.
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of patient positioning on quality of life is unknown.

Recommendation(s) for appropriate patient positioning

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
No recommendation made.		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?	YES	NO

Intervention 10 – Preoperative autologous donation

Key question(s): In patients undergoing surgery, what is the effect of PAD on transfusion incidence (allogeneic blood)?		Evidence table ref*: POQ3.I10.P1a
1. Evidence base		
1 level I SR (Henry 2001)[a] and 2 Level II RCTs (Bouchard 2008; Hashimoto 2007) Pivotal evidence – Henry 2001 (Level I; good quality); 11 RCTs (assessed RBCs only), all fair quality; N=1423, Most up-to-date search; includes largest number of studies Supportive evidence – Bouchard 2008 (Level II; fair quality); N=48, Adult patients undergoing cardiac surgery Supportive evidence – Hashimoto 2007 (Level II; poor quality); N=79, Adult patients undergoing liver graft procurement.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
There is significant overall heterogeneity between the trials in Henry 2001 (Phet=0.00052). The results are consistent between the subgroups in Henry 2001. The results from Bouchard (2008) were not significant. No patients in Hashimoto 2007 were transfused with allogeneic blood.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Pivotal evidence – Henry 2001 Any surgery – RR 0.36 (0.25, 0.51); 11 trials (N=1423) Cancer surgery – RR 0.49 (0.38, 0.63); 5 trials (N=950) Orthopaedic surgery – RR 0.21 (0.11, 0.43); 5 (N=425) Maxillofacial surgery – RR 0.02 (0.00, 0.28); 1 trial (N=48) Supportive evidence – Bouchard 2008[b] and Hashimoto 2007[c] (see Summary Table POQ3.I10.P1)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. Surgical operations assessed include cancer surgery, orthopaedic surgery, maxillofacial surgery, cardiac surgery, and liver graft procurement.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies were conducted in a hospital setting. The RCTs included in Henry 2001 were conducted in Germany, Greece, Japan, Sweden, the Netherlands, and the USA. Bouchard 2008 and Hashimoto 2007 were conducted in Canadian and Japanese hospitals respectively.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Thirteen level II studies with a moderate risk of bias
2. Consistency	B	Some inconsistency, which is mainly in orthopaedic surgery. Overall direction of effect consistent.
3. Clinical impact	A	The reduction in transfusion incidence associated with PAD is very large
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, preoperative autologous donation reduces the incidence of allogeneic RBC transfusion.

Abbreviations: PAD, Preoperative autologous donation; RCT, randomised controlled trial; RR, relative risk; SR, systematic review.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[a] Publication dated 2001 but includes update to January 2004

[b] Results from Bouchard 2008 – RR (people transfused with allogeneic blood products): 0.41 (0.15, 1.15); RR (people transfused with allogeneic blood): 0.06 (0.00, 1.02).

[c] Results from Hashimoto 2007 – RR 0 (0,0).

Key question(s): In patients undergoing surgery, what is the effect of PAD on transfusion incidence (allogeneic and/or autologous blood)?		Evidence table ref*: POQ3.I10.P1b
1. Evidence base		
1 level I SR (Henry 2001)[a] and 2 Level II RCTs (Bouchard 2008; Hashimoto 2007) Pivotal evidence – Henry 2001 (Level I; good quality); 11 RCTs (assessed RBCs only); N=1423 Most up-to-date search; includes largest number of studies Supportive evidence – Bouchard 2008 (Level II; fair quality); N=48 Adult patients undergoing cardiac surgery	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
There is significant overall heterogeneity between the trials in Henry 2001 (Phet<0.). The results are consistent between the subgroups in Henry 2001. The results from Bouchard (2008) were not significant.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Pivotal evidence – Henry 2001 Any surgery – RR 1.33 (1.10, 1.61); 9 trials (N=1232) Cancer surgery – RR 1.38 (1.20, 1.58); 5 trials (N=950) Orthopaedic surgery – RR 1.78 (0.61, 5.20); 3 trials (N=234) Maxillofacial surgery – RR 0 (0, 0); 1 trial (N=48) Supportive evidence – Bouchard 2008 (see Summary Table POQ3.I10.P1)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence is generalisable to an adult population who are undergoing elective surgery. Surgical operations assessed include cancer surgery, orthopaedic surgery, maxillofacial surgery, and cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies were conducted in a hospital setting. The RCTs included in Henry 2001 were conducted in Germany, Greece, Japan, Sweden, the Netherlands, and the USA. Bouchard 2008 was conducted in a Canadian hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

The CRG considered the conclusions from the Henry (2001) review, which outlines the potential for harm, offsetting benefits from preoperative autologous donation.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Thirteen level II studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	Substantial clinical impact
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss, preoperative autologous donation increases the overall incidence of blood transfusion.

Abbreviations: PAD, Preoperative autologous donation; RCT, randomised controlled trial; RR, relative risk; SR, systematic review.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[a] Publication dated 2001 but includes update to January 2004

POQ3.I10.P1 Characteristics and results of studies examining the effect of PAD on transfusion incidence.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Henry (2001)	Level I *Good*	11 trials N=1423	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Patients transfused with allogeneic blood	149/716 (21%)	375/707 (53%)	P<0.05	Phet<0.01
		9 trials N=1232				Patients transfused with allogeneic and/or autologous	496/620 (80%)	343/612 (56%)	P<0.05	Phet<0.01
Cancer surgery										
Henry (2001)	Level I *Good*	5 trials N=950	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Patients transfused with allogeneic blood	128/467 (27%)	280/483 (58%)	P<0.05	Phet=0.15
		5 trials N=950				Patients transfused with allogeneic and/or autologous	363/467 (78%)	260/483 (54%)	P<0.05	Phet=0.13
Orthopaedic surgery										
Henry (2001)	Level I *Good*	5 trials N=425	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Patients transfused with allogeneic blood	21/221 (10%)	75/204 (37%)	P<0.05	Phet=0.07
		3 trials N=234				Patients transfused with allogeneic and/or autologous	105/125 (84%)	43/109 (39%)	P>0.05	Phet<0.01
Maxillofacial surgery										
Henry (2001)	Level I *Good*	1 trial N=48	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Patients transfused with allogeneic blood	0/28 (0%)	20/20 (100%)	P<0.05	
		1 trial N=48				Patients transfused with allogeneic and/or autologous	28/28 (100%)	20/20 (100%)	NA	
Cardiac surgery										
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg). Blood was reinfused postoperatively	Patients transfused with autologous blood	6/25 (24%)	NA	NA	
						Patients transfused with allogeneic blood products	4/25 (16%)	9/23 (39%)	P=0.09	
						Patients transfused with allogeneic blood	0/25 (0%)	7/23 (30%)	P=0.05	

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Liver resection										
Hashimoto (2007)	Level II *Poor*	N=79	Adults undergoing liver graft procurement	Japanese hospital	Blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement.	Patients transfused with allogeneic blood	0/40 (0%)	0/39 (0%)	Not estimable	
Studies with a transfusion protocol										
Henry (2001)	Level I *Good*	7 trials N=1206	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Patients transfused with allogeneic blood	138/595 (23%)	299/611 (49%)	P<0.05	Phet=0.18
		5 trials N=1015				Patients transfused with allogeneic and/or autologous	384/499 (77%)	267/516 (52%)	P<0.05	Phet<0.01
Studies without a transfusion protocol										
Henry (2001)	Level I *Good*	4 trials N=217	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Patients transfused with allogeneic blood	11/121 (9%)	76/96 (79%)	P<0.05	Phet=0.08
		4 trials N=217				Patients transfused with allogeneic and/or autologous	112/121 (93%)	76/96 (79%)	P>0.05	Phet<0.001

Abbreviations: PAD, preoperative autologous donation.

Key question(s): In patients undergoing surgery, what is the effect of PAD on transfusion volume?		Evidence table ref*: POQ3.I10.P2
1. Evidence base		
1 Level II RCT (Bouchard 2008); Fair quality; N=48 It is unclear whether allocation to treatment groups was concealed from those responsible for recruiting subjects. The treatment arms had similar demographic characteristics. Neither the patient nor the surgeon was blinded to the group assignment; however, the ICU intensivist, nurses, and residents were blinded. A transfusion protocol was uses. All analyses were conducted ITT. PAD was not completed in 2 patients (8%) because of worsened angina pectoris. NB: Level I evidence (Henry 2001) did not report this outcome.[a]	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Bouchard 2008 (N=48) Autologous blood (mean [SD]: PAD vs. control), units: 2 (1.2) vs. 0 (0) Allogeneic blood (mean [SD]: PAD vs. control), units: 0 (0) vs. 2 (1.2) Fresh frozen plasma (mean difference [SD]), units: 4.0 (0) vs. 2.8 (1) Platelets (mean difference [SD]), units: 4.3 (2.9) vs. 6 (0) Cryoprecipitate (mean difference [SD]), units: 0 (0) vs 10 (0)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in adults undergoing elective cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in a Canadian hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One level II study with moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	B	Not statistically significant
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, preoperative autologous donation may reduce the volume of allogeneic blood transfusion.

In adult patients undergoing surgery in which substantial blood loss is anticipated, preoperative autologous donation does not appear to have an effect on the overall volume of blood transfusion.

Abbreviations: ICU, intensive care unit; ITT, intention-to-treat; NA, not applicable; PAD, preoperative autologous donation; RCT, randomised controlled trial; SD, standard deviation.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[a] Transfusion volume was one the primary outcomes in Henry 2001; however, none of the RCTs provided sufficient detail on this outcome for meta-analysis.

POQ3.I10.P2 Characteristics and results of studies examining the effect of PAD on transfusion volume.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Henry (2001)	Level I *Good*	11 trials N=1423	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Mean (SD), units	NR	NR	NR	None of the included RCTs provided sufficient evidence to conduct a meta-analysis.
Autologous blood										
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg) was withdrawn preoperatively. Blood was reinfused postoperatively	Mean (SD), units	2 (1.2)	0 (0)	Not estimable	
Allogeneic blood										
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg) was withdrawn preoperatively. Blood was reinfused postoperatively	Mean (SD), units	0 (0)	2 (1.2)	Not estimable	
Fresh frozen plasma										
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg) was withdrawn preoperatively. Blood was reinfused postoperatively	Mean (SD), units	4 (0)	2.8 (1)	Not estimable	
Platelets										
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg) was withdrawn preoperatively. Blood was reinfused postoperatively	Mean (SD), units	4.3 (2.9)	6 (0)	Not estimable	

Cryoprecipitate										
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg) was withdrawn preoperatively. Blood was reinfused postoperatively	Mean (SD), units	0 (0)	10	Not estimable	

Abbreviations: NR, not reported; PAD, preoperative autologous donation; RCT, randomised controlled trial; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of PAD on blood loss?		Evidence table ref*: POQ3.I10.P3
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Bouchard 2008 (Level II; fair quality); N=48 Allocation concealment not reported. Neither the patient nor the surgeon was blinded to the group assignment; however, the ICU intensivist, nurses, and residents were blinded. A transfusion protocol was uses. Analyses conducted ITT. Hashimoto 2007 (Level II; poor quality); N=79 Allocation concealment not reported. The study was not blinded. No transfusion protocol was reported. The study was not conducted ITT[a].	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
In both studies there was no significant difference in operative blood loss; however there was a significant difference in the blood loss during transection between PAD and control in Hashimoto 2007.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Bouchard 2008 Operative blood loss – mean difference -34 (-171, 102); P=0.62 Postoperative blood loss – mean difference 27 (-302, 355); P=0.88 Hashimoto 2007 Operative blood loss – mean difference -37 (-101, 27); P=0.25 Transection blood loss – mean difference -90 (-172, -8); P=0.031	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Bouchard 2008 was conducted in patients undergoing cardiac surgery. Hashimoto 2007 was conducted in patients undergoing liver resection.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Bouchard 2008 was conducted in a Canadian hospital and Hashimoto 2007 was conducted in a Japanese hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two level II studies of fair and poor quality and small size (N=48 and N=79)
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question (refer to clinical impact)
3. Clinical impact	D	No statistically significant difference in operative blood loss. A small, but significant, difference in transection blood loss.
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied. One cardiac study and one liver graft procurement
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats. Studies conducted in Canada and Japan.

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of preoperative autologous donation on blood loss is uncertain.

Abbreviations: ICU, intensive care unit; ITT, intention to treat; PAD, preoperative autologous donation.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[a] One patient in the control group was excluded from analysis after randomisation because the operation was stopped due to an asthmatic attack.

POQ3.I10.P3 Characteristics and results of studies examining the effect of PAD on outcome blood loss.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg). Blood was reinfused postoperatively	Operative blood loss Mean difference (95% CI), mL	-34 (-171, 102)		P=0.62	
						Postoperative blood loss Mean difference (95% CI), mL	27 (-302, 355)		P=0.88	
Hashimoto (2007)	Level II *Poor*	N=79	Adults undergoing liver graft procurement	Japanese hospital	Blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement.	Operative blood loss Mean difference (95% CI), mL	-37 (-101, 27)		P=0.25	
						Transection blood loss Mean difference (95% CI), mL	-90 (-172, -8)		P=0.031	

Abbreviations: CI, confidence interval; PAD, preoperative autologous donation.

Key question(s): In patients undergoing surgery, what is the effect of PAD on mortality?		Evidence table ref*: POQ3.I10.P4
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
1 Level II evidence RCT (Hashimoto 2007). Poor quality. (N=79; 40 PAD, 39 control) It is unclear whether allocation was concealed from those in charge of recruiting subjects. Baseline characteristics were similar between treatment groups. The patients and surgeons were not blinded to randomisation results. No transfusion protocol was reported. One patient in the control group was excluded from analysis after randomisation because the operation was stopped due to an asthmatic attack Henry 2001 (level I; good quality) reported "insufficient evidence" for an association between PAD and mortality but did not report any more detail.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The mortality rate was 0% in both treatment arms.	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study population was patients undergoing liver graft procurement.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in a Japanese university hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Included studies were underpowered to detect a mortality difference.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Not statistically significant
4. Generalisability	C	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of preoperative autologous donation on mortality is uncertain.

Abbreviations: PAD, preoperative autologous donation; RCT, randomised controlled trial.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I10.P4 Characteristics and results of studies examining the effect of PAD on mortality.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Henry (2001)	Level I *Good*	11 trials N=1423	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Mortality	NR	NR	NR	The authors found "insufficient evidence" for any association between PAD and mortality.
Hashimoto (2007)	Level I *Good*	N=79	Adult population undergoing liver resection	Japanese hospital	PAD: Blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement.	Mortality	0/40 (0%)	0/39 (0%)	not estimable	

Abbreviations: NR, not reported; PAD, preoperative autologous donation.

Key question(s): In patients undergoing surgery, what is the effect of PAD on morbidity?		Evidence table ref*: POQ3.I10.P5
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Evidence for rate of infection: 1 Level I SR (Henry 2001); good quality; N=621 Evidence for rate of thrombosis: 1 level I SR (Henry 2001); good quality; N=250 Evidence for rate of stroke, DVP, and pulmonary embolus: 1 level I SR (Henry 2001); good quality; N=NR Evidence for rate of bile leak: 1 level II RCT (Hashimoto 2007); poor quality; N=79 Evidence for rate of intra-abdominal bleeding: 1 level II RCT (Hashimoto 2007); poor quality; N=79	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Infection: one trial reported in Henry 2001 found that the infection rate for patients with PAD was significantly lower than patients without PAD (RR 0.44; 95% CI: 0.20, 0.98). The other two trials reporting infection as an outcome found no significant difference between PAD and no PAD. The level of heterogeneity was not significant (Phet=0.07). Thrombosis: all three trials found no significant difference. The level of heterogeneity between the trials was not significant (Phet=0.53)	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Infection – RR 0.70 (0.34, 1.43); 3 trials (N=621) Thrombosis – RR 0.82 (0.21, 3.13); 3 trials (N=250) Bile leak – RR 0.33 (0.01, 7.75); 1 trial (N=79) Intra-abdominal bleeding – RR 0.33 (0.01, 7.75); 1 trial (N=79)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to an adult population who are undergoing elective surgery. Surgical operations assessed include cancer surgery, orthopaedic surgery, maxillofacial surgery, and liver graft procurement.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
All the studies were conducted in a hospital setting. The RCTs included in Henry 2001 were conducted in Germany, Greece, Japan, Sweden, the Netherlands, and the USA. Hashimoto 2007 was conducted in a Japanese hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The CRG noted that the studies used varying definitions and sources of infection. Studies were of poor methodological quality and were underpowered for morbidity outcomes.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Level II studies with a moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	D	Not statistically significant
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect on preoperative autologous donation on morbidity is uncertain.

Abbreviations: DVP, deep vein thrombosis; NR, not reported; PAD, preoperative autologous donation; NR, not reported; RCT, randomised controlled trials; RR, relative risk; SR, systematic review.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I10.P5 Characteristics and results of studies examining the effect of PAD on morbidity.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Henry (2001)	Level I *Good*	3 trials N=621	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Infection	74/309 (24%)	81/312 (26%)	P>0.05	Phet=0.07
		3 trials N=250	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Thrombosis	6/140 (4%)	3/110 (3%)	P>0.05	Phet=0.53
		NR	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Other adverse events	NR	NR	NR	Insufficient data for stroke, DVP, and pulmonary embolus
Hashimoto (2007)	Level II *Poor*	N=79	Adults undergoing liver graft procurement	Japanese hospital	Blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement.	Bile leak	0/40 (0%)	1/39 (3%)	P=0.49	
						Intra-abdominal bleeding	0/40 (0%)	1/39 (3%)	P=0.49	

Abbreviations: DVP, deep vein thrombosis; NR, not reported; PAD, preoperative autologous donation.

Key question(s): In patients undergoing surgery, what is the effect of administration of PAD on quality of life?		Evidence table ref*: POQ3.I10.P6
1. Evidence base		
No evidence found	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	NA	
2. Consistency	NA	
3. Clinical impact	NA	
4. Generalisability	NA	
5. Applicability	NA	

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of PAD on quality of life is unknown.

Abbreviations: PAD, preoperative autologous donation.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

Key question(s): In patients undergoing surgery, what is the effect of PAD on change in haemoglobin concentration		Evidence table ref*: POQ3.I10.S1
1. Evidence base		
Henry 2001 (Level I; good quality); 5 RCTs (assessed RBCs only); N=534 Most up-to-date search; includes largest number of studies (only reports preoperative haemoglobin concentration) Bouchard 2008 (Level II; fair quality); N=48 Adult patients undergoing cardiac surgery. Reports pre- and postoperative haemoglobin concentration. Hashimoto 2007 (Level II; poor quality); N=79 Adult patients undergoing liver graft procurement. (only reports preoperative haemoglobin concentration) NB: the timeframe between PAD and surgery was not reported in either Henry 2001, Bouchard 2008, or Hashimoto 2007.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Preoperative haemoglobin concentration There is a significant level of heterogeneity between the trials in Henry 2001 (Phet=0.004). The results from Henry 2001 do not agree with the results from Bouchard 2008 and Hashimoto 2007. Postoperative haemoglobin concentration Only one of the studies (Bouchard 2008) reported postoperative haemoglobin concentration as an outcome.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Henry 2001 – mean difference in preoperative concentration between PAD and control, -1.16 (-1.60, -0.73) Bouchard 2008 – There was no significant difference between PAD and control at any time point. Mean difference: Preoperative, -0.60 (-1.36, 0.16); 24 hours postoperative, -0.40 (-1.11, 0.31); 5 days postoperative, -0.50 (-1.18, 0.18) Hashimoto 2007 – Median (IQR) preoperative haemoglobin concentration, PAD vs. control: 13.0 (11.0 to 15.7) vs. 13.6 (11.6 to 15.9)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalisability		
The evidence for difference in preoperative haemoglobin concentration between PAD and control is generalisable to an adult population who are undergoing elective surgery. Surgical operations assessed include cancer surgery, orthopaedic surgery, maxillofacial surgery, cardiac surgery, and liver graft procurement. The evidence for difference in postoperative haemoglobin concentration between PAD and control comes from one trial of patients undergoing cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
All the studies were conducted in a hospital setting. The RCTs included in Henry 2001 were conducted in Germany, Greece, Japan, Sweden, the Netherlands, and the USA. Bouchard 2008 and Hashimoto 2007 were conducted in Canadian and Japanese hospitals respectively.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Seven level II studies with a moderate risk of bias
2. Consistency	B	There is a significant degree of heterogeneity regarding
3. Clinical impact	C	PAD is associated with a moderate decrease in preoperative haemoglobin concentration compared with control
4. Generalisability	B	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, preoperative autologous donation reduces preoperative haemoglobin concentration.

Abbreviations: IQR, interquartile range; PAD, preoperative autologous donation; RCT, randomised controlled trial.
* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD
Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life
Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I10.S1 Characteristics and results of studies examining the effect of PAD on haemoglobin concentration.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Henry (2001)	Level I *Good*	5 trials (2 in orthopaedic surgery and 3 in surgery for cancer) N=534	Adult patients undergoing any elective surgery	Studies conducted in developed countries	PAD vs standard care	Preoperative Hb concentration. Mean difference (95% CI), g/dL	-1.16 (-1.60, -0.73)		P<0.05	Phet=0.004
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg). Blood was reinfused postoperatively	Preoperative Hb concentration. Mean difference (95% CI), g/dL	-0.60 (-1.36, 0.16)		P=0.12	
						Hb concentration 24 hours after surgery. Mean difference (95% CI), g/dL	-0.40 (-1.11, 0.31)		P=0.27	
						Hb concentration 5 days after surgery. Mean difference (95% CI), g/dL	-0.50 (-1.18, 0.18)		P=0.15	
Hashimoto (2007)	Level II *Poor*	N=79	Adults undergoing liver graft procurement	Japanese hospital	Blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement.	Preoperative Hb concentration. Median (IQR), g/dL	13.0 (11.0 to 15.7)	13.6 (11.6 to 15.9)	P=0.455	

Abbreviations: CI, confidence interval; IQR, interquartile range; Hb, haemoglobin; PAD, preoperative autologous donation.

Key question(s): In patients undergoing surgery, what is the effect of administration of PAD on coagulation status?		Evidence table ref*: POQ3.I10.S3
1. Evidence base		
Two Level II studies: Bouchard 2009 (fair quality; N=48); Hashimoto 2007 (poor quality; N=79) Bouchard 2009 reports prothrombin time, and fibrinogen concentration Hashimoto 2007 reports prothrombin time and INR	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Both studies found no significant impact on prothrombin time or INR. Bouchard 2009 is the only study that reports fibrinogen concentration.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
See Summary Table POQ3.I10.S3.	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
Bouchard 2008 was conducted in patients undergoing cardiac surgery. Hashimoto 2007 was conducted in patients undergoing liver resection.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Bouchard 2008 was conducted in a Canadian hospital and Hashimoto 2007 was conducted in a Japanese hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two Level II studies with moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	No statistically significant impact on prothrombin time
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, preoperative autologous donation does not appear to have an effect on prothrombin time.

Abbreviations: INR, international normalised ratio; PAD, preoperative autologous donation.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I10.S3 Characteristics and results of studies examining the effect of PAD on coagulation status.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg). Blood was reinfused postoperatively	Preoperative prothrombin time (mean [SD]), seconds	9.7 (2.8)	9.4 (1.1)	P=0.62	
						Prothrombin time 30 minutes after surgery (mean [SD]), seconds	13.2 (3.9)	13.5 (2.2)	P=0.74	
						Prothrombin time 24 hours after surgery (mean [SD]), seconds	10.3 (1.3)	10.9 (1.7)	P=0.17	
						Preoperative fibrinogen concentration (mean [SD]), g/L	4.3 (1.5)	3.1 (0.9)	P=0.0007	
						Fibrinogen concentration 30 minutes after surgery (mean [SD]), g/L	3.0 (0.9)	2.6 (0.7)	P=0.08	
						Fibrinogen concentration 24 hours after surgery (mean [SD]), g/L	6.2 (1.3)	5.1 (1.2)	P=0.002	
Hashimoto (2007)	Level II *Poor*	N=79	Adults undergoing liver graft procurement	Japanese hospital	Blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement.	Prothrombin time 24 hours after surgery (median [IQR]), seconds	12.3 (9.6 to 15.9)	12.5 (10.5 to 15.0)	P=0.280	
						Preoperative INR (median [IQR])	1.11 (0.95 to 1.34)	1.10 (0.91 to 1.31)	P=0.350	
						INR 24 hours postoperative (median [IQR])	1.76 (1.30 to 2.37)	1.77 (1.29 to 2.32)	P=0.456	

Abbreviations: IQR, interquartile range; PAD, preoperative autologous donation; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of PAD on length of hospital stay?		Evidence table ref*: POQ3.I10.S5
1. Evidence base		
Bouchard 2008 (Level II; fair quality); N=48 Allocation concealment not reported. Neither the patient nor the surgeon was blinded to the group assignment; however, the ICU intensivist, nurses, and residents were blinded. A transfusion protocol was uses. Analyses conducted ITT. Hashimoto 2007 (Level II; poor quality); N=79 Allocation concealment not reported. The study was not blinded. No transfusion protocol was reported. The study was not conducted ITT[a].	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
Both studies found no significant effect of administration of PAD on length of hospital stay.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Bouchard 2008 Mean difference (95% CI), days: 0.00 (-0.51, 0.51); P=1.00 Hashimoto 2007 PAD vs. control (Median [IQR]), days: 14 (10 to 36) vs. 14 (11 to 46); P=0.476	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
Bouchard 2008 was conducted in patients undergoing cardiac surgery. Hashimoto 2007 was conducted in patients undergoing liver resection.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Bouchard 2008 was conducted in a Canadian hospital and Hashimoto 2007 was conducted in a Japanese hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	Two level II studies with a moderate risk of bias
2. Consistency	A	Both studies showed consistent results
3. Clinical impact	D	Not statistically significant
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of preoperative autologous donation on length of hospital stay is uncertain.

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; ITT, intention-to-treat; PAD, preoperative autologous donation.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

[a] One patient in the control group was excluded from analysis after randomisation because the operation was stopped due to an asthmatic attack.

POQ3.I10.S5 Characteristics and results of studies examining the effect of PAD on hospital length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg). Blood was reinfused postoperatively	Mean difference (95% SD), days	0.00 (-0.51, 0.51)		P=1.00	
Hashimoto (2007)	Level II *Poor*	N=79	Adults undergoing liver graft procurement	Japanese hospital	Blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement.	Median (IQR), days	14 (10 to 36)	14 (11 to 46)	P=0.476	

Abbreviations: IQR, interquartile range; PAD, preoperative autologous donation; SD, standard deviation.

Key question(s): In patients undergoing surgery, what is the effect of PAD on ICU admission and length of stay?		Evidence table ref*: POQ3.I10.S6
1. Evidence base		
Bouchard 2008 (Level II; fair); N=48 Allocation concealment not reported. Neither the patient nor the surgeon was blinded to the group assignment; however, the ICU intensivist, nurses, and residents were blinded. A transfusion protocol was uses. Analyses conducted ITT.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact		
Mean difference (95% CI): 0.00 (-3.34, 0.34)	A	Very large
	B	Substantial
	C	Moderate
	D	No difference
4. Generalisability		
Study was conducted in adults undergoing elective cardiac surgery.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability		
Study was conducted in a Canadian hospital.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Not statistically significant
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of preoperative autologous donation on length of ICU stay is uncertain.

Abbreviations: CI, confidence interval; ICU, intensive care unit; ITT, intention-to-treat; PAD, preoperative autologous donation.

* Interventions: I1 = ANH, I2 = intraoperative cell salvage, I3 = perioperative ANH and intraoperative cell salvage, I4 = postoperative cell salvage, I5 = deliberate induced hypotension, I6 = prevention of hypothermia, I7 = point-of-care testing for coagulation status and haemoglobin, I8 = administration of antifibrinolytics (tranexamic acid, EACA, aprotinin) and DDAVP, I9 = appropriate patient positioning, I10 = PAD

Primary outcomes: P1 = transfusion incidence, P2 = transfusion volume, P3 = blood loss, P4 = mortality, P5 = morbidity, P6 = quality of life

Secondary outcomes: S1 = change in haemoglobin, S2 = reoperation for bleeding, S3 = correction/prevention of DIC and coagulopathy, S4 = cost, S5 = hospital length of stay, S6 = ICU admission and length of stay, S7 = hospital readmission

POQ3.I10.S6 Characteristics and results of studies examining the effect of PAD on outcome ICU admission and length of stay.

Study	Level of evidence *Quality*	No. of trials / sample size	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			Notes
							Intervention	Comparator	p-value	
Bouchard (2008)	Level II *Fair*	N=48	Adults undergoing elective cardiac surgery	Canadian hospital	Two units of 350 mL each (or 6mL/kg when the patent's weight was below 60 kg). Blood was reinfused postoperatively	Length of ICU stay, days Mean difference (95% CI)	0.00 (-0.34, 0.34)		P=1.00	

Abbreviations: CI, confidence interval; ICU, intensive care unit; PAD, preoperative autologous donation.

Recommendation(s) for preoperative autologous donation

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE	RELEVANT EVIDENCE TABLE
The *routine* use of preoperative autologous donation is not recommended because, although it reduces the risk of allogeneic RBC transfusion, it increases the risk of receiving any RBC transfusion (allogeneic and autologous).	C	PO3.I10.P1

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Routine use of PAD should reduce.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Potential cost savings; frees up ARCBS time.		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Existence of MBS item number.		
What could help to facilitate implementation of the recommendation?		
Successful lobbying to remove MBS item number.		

Appendix E: Quality analyses

Intervention 1 – Acute normovolemic haemodilution

Level I evidence

Citation	Bryson GL, Laupacis A, and Wells GA. (1998) Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. Anesthesia and Analgesia 86:9-15.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
N	Were the sources of heterogeneity explored?
Comments	The SR includes both RCTs and observational studies, however the results are evaluated separately by study type.
Overall assessment	Fair

Citation	Gurusamy KS, Li J, Sharma D, and Davidson BR. (2009) Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database of Systematic Reviews: Reviews 2009. Issue. 4
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Laupacis A and Fergusson D. (1998) The efficacy of technologies to minimise perioperative allogeneic transfusion (Structured abstract). Kluwer. Academic Publishers.17-36.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
N	Were the sources of heterogeneity explored?
Comments	Baseline characteristics and use of transfusion protocol not reported.
Overall assessment	Fair

Citation	Segal JB, Blasco-Colmenares E, Norris EJ, and Guallar E. (2004) Preoperative acute normovolemic hemodilution: A meta-analysis. Transfusion 44:632-644.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
N	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Authors did not analyse data by surgery type or use of transfusion protocol.
Overall assessment	Fair

Level II evidence

Citation	Akhlagh SH, Chohedri AH, Bazojoo A, and Nemati MH. (2007) A comparison of total amount of blood needed in patients taking autologous or homologous blood transfusion in coronary artery bypass grafting: A clinical randomized case-control trial. Pakistan Journal of Medical Sciences 23:542-545.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
NR	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Although the study reports the total number of patients in the study it does not specify the numbers randomised to treatment arms. No transfusion protocol was reported.
Overall assessment	Poor

Citation	Bennett J, Haynes S, Torella F, Grainger H, and McCollum C. (2006) Acute normovolemic hemodilution in moderate blood loss surgery: A randomized controlled trial. Transfusion 46:1097-1103.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Neither the anaesthetist nor the surgical team could be blinded.
Overall assessment	Fair

Citation	Casati V, Speziali G, D'Alessandro C, Cianchi C, Antonietta Grasso M, Spagnolo S, and Sandrelli L. (2002) Intraoperative low-volume acute normovolemic hemodilution in adult open-heart surgery. Anesthesiology 97:367-373.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Poor

Citation	Casati V, Benussi S, Sandrelli L, Grasso MA, Spagnolo S, and D'Angelo A. (2004) Intraoperative Moderate Acute Norvolemic Hemodilution Associated with a Comprehensive Blood-Sparing Protocol in Off-Pump Coronary Surgery. Anesthesia and Analgesia 98:1217-1223.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Hohn L, Schweizer A, Licker M, and Morel DR. (2002) Absence of beneficial effect of acute normovolemic hemodilution combined with aprotinin on allogeneic blood transfusion requirements in cardiac surgery. Anesthesiology 96:276-282.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Poor

Citation	Friesen RH, Perryman KM, Weigers KR, Mitchell MB, and Friesen RM. (2006) A trial of fresh autologous whole blood to treat dilutional coagulopathy following cardiopulmonary bypass in infants. Paediatric Anaesthesia 16:429-435.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Jarnagin WR, Gonen M, Maithel SK, Fong Y, DAngelica MI, Dematteo RP, Grant F, Wuest D, Kundu K, Blumgart LH, and Fischer M. (2008) A prospective randomized trial of acute normovolemic hemodilution compared to standard intraoperative management in patients undergoing major hepatic resection. Annals of Surgery 248:360-368.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Juelsgaard P, Moller MB, and Larsen UT. (2002) Preoperative acute normovolaemic hemodilution (ANH) in combination with hypotensive epidural anaesthesia (HEA) during knee arthroplasty surgery. No effect on transfusion rate. A randomized controlled trial [ISRCTN87597684]. BMC Anesthesiology 2.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Lim YJ, Kim CS, Bahk JH, Ham BM, and Do SH. (2003) Clinical trial of esmolol-induced controlled hypotension with or without acute normovolemic hemodilution in spinal surgery. Acta Anaesthesiologica Scandinavica 47:74-78.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Matot I, Scheinin O, Jurim O, and Eid A. (2002) Effectiveness of acute normovolemic hemodilution to minimize allogeneic blood transfusion in major liver resections. Anesthesiology 97:794-800.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Obasi C, Arendt J, and Antoszewski Z. (2006) An assessment of the efficacy of preoperative controlled haemodilution in the perioperative management of patients including the elderly. Chirurgia Polska 8:111-124.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
N	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Very little methodological detail. Assessed multiple surgery types without evaluating heterogeneity. No transfusion protocol.
Overall assessment	Poor

Citation	Sanders G, Mellor N, Rickards K, Rushton A, Christie I, Nicholl J, Copplestone A, and Hosie K. (2004) Prospective randomized controlled trial of acute normovolaemic haemodilution in major gastrointestinal surgery. British Journal of Anaesthesia 93:775-781.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Saricaoglu F, Akinci SB, and Aypar U. (2005) The effect of acute normovolemic hemodilution and acute hypervolemic hemodilution on coagulation and allogeneic transfusion. Saudi Medical Journal 26:792-798.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Good

Citation	Wolowczyk L, Nevin M, Smith FCT, Baird RN, and Lamont PM. (2003) Haemodilutional effect of standard fluid management limits the effectiveness of acute normovolaemic haemodilution in AAA surgery - Results of a pilot trial. European Journal of Vascular and Endovascular 26:405-411.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Intervention 2 – Intraoperative cell salvage

Level I evidence

Citation	Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine 14:123-144.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Number of participants in studies not reported
Overall assessment	Fair

Citation	Carless PA, Henry DA, Moxey AJ, O'connell DL, Brown T, and Fergusson DA. (2006) Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane database of reviews (Online)CD001888.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Includes intra- and postoperative data
Overall assessment	Good

Citation	Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, and McCollum C. (2006) Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: A systematic review and economic model. Health Technology Assessment 10:1-114.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Huet C, Salmi R, Fergusson D, Koopman-Van Gemert AWMM, Rubens F, and Laupacis A. (1999) A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. Anesthesia and Analgesia 89:861-869.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Takagi H, Sekino S, Kato T, Matsuno Y, and Umemoto T. (2007) Intraoperative autotransfusion in abdominal aortic aneurysm surgery: meta-analysis of randomized controlled trials (Structured abstract). Archives of Surgery 142:1098-1101.
Y	A. Was a clinical question clearly defined?
N	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
	E. Were the characteristics and results if the individual studies appropriately summarised?
	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Specific search strategy not described,
Overall assessment	Fair

Level II evidence

Citation	Bowley DM, Barker P, and Boffard KD. (2006) Intraoperative blood salvage in penetrating abdominal trauma: A randomised, controlled trial. World Journal of Surgery 30:1074-1080.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	It is unclear whether the analysis was ITT
Overall assessment	Fair

Citation	Damgaard S and Steinbruchel DA. (2006) Autotransfusion with cell saver for off-pump coronary artery bypass surgery: A randomized trial. Scandinavian Cardiovascular Journal 40:194-198.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	The surgical and anesthetic team were blinded during the operation, but not after. The ICU staff were blinded.
Overall assessment	Good

Citation	Goel P, Pannu H, Mohan D, and Arora R. (2007) Efficacy of cell saver in reducing homologous blood transfusions during OPCAB surgery: A prospective randomized trial. Transfusion Medicine 17:285-289.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Mercer KG, Spark JI, Berridge DC, Kent PJ, and Scott DJA. (2004) Randomized clinical trial of intraoperative autotransfusion in surgery for abdominal aortic aneurysm. British Journal of Surgery 91:1443-1448.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Good

Citation	Murphy GJ, Rogers CS, Lansdowne WB, Channon I, Alwair H, Cohen A, Caputo M, and Angelini GD. (2005) Safety, efficacy, and cost of intraoperative cell salvage and autotransfusion after off-pump coronary artery bypass surgery: A randomized trial. Journal of Thoracic and Cardiovascular 130:20-28.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Niranjan G, Asimakopoulos G, Karagounis A, Cockerill G, Thompson M, and Chandrasekaran V. (2006) Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on- versus off-cardiopulmonary bypass: a randomised trial. European Journal of Cardio-thoracic Surgery 30:271-277.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Good

Citation	Selo-Ojeme DO and Feyi-Waboso PA. (2007) Salvage autotransfusion versus homologous blood transfusion for ruptured ectopic pregnancy. International Journal of Gynecology and Obstetrics 96:108-111.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	No transfusion protocol was used.
Overall assessment	Fair

Citation	Wiefferink A, Weerwind PW, van Heerde W, Teerenstra S, Noyez L, de Pauw BE, and Brouwer RM. (2007) Autotransfusion management during and after cardiopulmonary bypass alters fibrin degradation and transfusion requirements. The Journal of Extra-corporeal Technology 39:66-70.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
N	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	No transfusion protocol was reported, low
Overall assessment	Fair

Citation	Zhang XL, Qian BH, and Luo QF. (2004) Effects of blood transfusion modes during perioperative period on prognosis of patients with scoliosis. Chinese Journal of Clinical Rehabilitation 8:7308-7310.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	No transfusion protocol was used; insufficient detail provided for many of the outcomes; surgical procedure not described; although paper states that there was no difference in baseline characteristics, the baseline values themselves were not reported.
Overall assessment	Poor

Intervention 3 – Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage

Level II evidence

Citation	Haynes SL, Torella F, Wong JCL, Dalrymple K, James M, and McCollum CN. (2002) Economic evaluation of a randomized clinical trial of haemodilution with cell salvage in aortic surgery. British Journal of Surgery 89:731-736.
NA	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NA	B. Was the study double-blinded?
NA	C. Were patient characteristics and demographics similar between treatment arms at baseline?
NA	D. Were all randomised patients included in the analysis?
NA	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	Authors did not conduct subgroup analysis by type of aortic surgery.
Overall assessment	Fair (See Wong et al [2002])

Citation	McGill N, O'Shaughnessy D, Pickering R, Herbertson M, and Gill R. (2002) Mechanical methods of reducing blood transfusion in cardiac surgery: Randomised controlled trial. British Medical Journal 324:1299-1302.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Wong JC, Torella F, Haynes SL, Dalrymple K, Mortimer AJ, McCollum CN, and ATIS I. (2002) Autologous versus allogeneic transfusion in aortic surgery: a multicenter randomized clinical trial. Annals of surgery 235:145-151.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	A transfusion protocol was used
Overall assessment	Fair

Intervention 4 – Postoperative cell salvage

Level I evidence

Citation	Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine 14:123-144.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Number of participants in studies not reported
Overall assessment	Fair

Citation	Carless PA, Henry DA, Moxey AJ, O'connell DL, Brown T, and Fergusson DA. (2006) Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane database of reviews (Online)CD001888.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Includes intra- and postoperative data
Overall assessment	Good

Citation	Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, and McCollum C. (2006) Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: A systematic review and economic model. Health Technology Assessment 10:1-114.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Duffy G and Neal KR. (1996) Differences in postoperative infection rates between patients receiving autologous and allogeneic blood transfusion: a meta-analysis of published randomized and nonrandomized studies (Structured abstract). Transfusion Medicine 6:325-328.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
NA	Were the methods for pooling the data appropriate?
NA	Were the sources of heterogeneity explored?
Comments	Limited trial info provided
Overall assessment	Fair

Citation	Huet C, Salmi R, Fergusson D, Koopman-Van Gemert AWMM, Rubens F, and Laupacis A. (1999) A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. Anesthesia and Analgesia 89:861-869.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
N	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Fair

Level II evidence

Citation	Amin A, Watson A, Mangwani J, Nawabi D, Ahluwalia R, and Loeffler M. (2008) A prospective randomised controlled trial of autologous retransfusion in total knee replacement. Journal of Bone and Joint - Series B 90:451-454.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Cheng SC, Hung TS, and Tse PY. (2005) Investigation of the use of drained blood reinfusion after total knee arthroplasty: a prospective randomised controlled study. Journal of Orthopaedic Surgery (Hong Kong) 13:120-124.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Near the end of each operation, the corresponding envelope for each patient was opened, and the surgeon was informed at the time of drain insertion to achieve a single-blind effect. The control group had a larger proportion of patients with a pre-morbid condition (65% vs 54%) and a larger proportion of males compared with the reinfusion group (35% vs 23%). However, these differences were not significant.
Overall assessment	Fair

Citation	Zacharopoulos A, Apostolopoulos A, and Kyriakidis A. (2007) The effectiveness of reinfusion after total knee replacement. A prospective randomised controlled study. International Orthopaedics 31:303-308.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
N	C. Were patient characteristics and demographics similar between treatment arms at baseline?
NR	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	The study did not report use of a transfusion protocol. Clinical outcomes and patient demographics were insufficiently reported. It is unclear whether all patients were included in the analysis. The authors report results as “average” without clarifying whether they are referring to mean or median.
Overall assessment	Poor

Intervention 5 – Deliberate induced hypotension

Level I evidence

Citation	Paul JE, Ling E, Lalonde C, Thabane L. Deliberate hypotension in orthopedic surgery reduces blood loss and transfusion requirements: A meta-analysis of randomized controlled trials. Can J Anesth 2007;54(10):799-810.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	F. Were the methods for pooling the data appropriate?
Y	G. Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Level II evidence

Citation	Boldt J, Weber A, Mailer K, Papsdorf M, Schuster P. Acute normovolaemic haemodilution vs controlled hypotension for reducing the use of allogeneic blood in patients undergoing radical prostatectomy. Br J Anaesth 1999;82(2):170-174.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Good.

Citation	Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive anaesthesia. Br J Anaesth 2006;96(6):727-731.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	The statistical analyses were appropriate and presented well. However, it does not provide an assessment/discussion of possible limitations or bias in this study.
Overall assessment	Good

Citation	Fredin H, Gustafson C, Rosberg B. Hypotensive anesthesia, thromboprophylaxis and postoperative thromboembolism in total hip arthroplasty. Acta Anaesthesiol Scand 1984;28(5):503-507.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	However, it is lacking details regarding the randomisation and blinding procedure. Statistical analyses performed were appropriate and well presented. Discussion did not address the presence of possible biases in the study.
Overall assessment	Fair

Citation	Jacobi KE, Bohm BE, Rickauer AJ, Jacobi C. Moderate controlled hypotension with sodium nitroprusside does not improve surgical conditions or decrease blood loss in endoscopic sinus surgery. J Clin Anesth 2000;12(3):202-207.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NR	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	This study did not include a description of the blinding methods employed, if any. Modest sample size (n=32).
Overall assessment	Fair

Citation	Karakaya D, Ustun E, Tur A, Baris S, Sarihasan B, Sahinoglu H, Guldogus F. Acute normovolemic hemodilution and nitroglycerin-induced hypotension: Comparative effects on tissue oxygenation and allogeneic blood transfusion requirement in total hip arthroplasty. J Clin Anesth 1999;11(5):368-374.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NR	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	This RCT did not describe the blinding method employed, if any. Due to the small sample size (n=10 per group), non-parametric methods should have been used.
Overall assessment	Fair

Citation	Kop EC, Spauwen PHM, Kouwenberg PPGM, Heymans FJM, van Beem HBH. Influence of controlled hypotension versus normotension on amount of blood loss during breast reduction. J Plast Reconstr Aesthetic Surg 2009;62(2):200-205.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	The discussion included an assessment of possible limitations such as the in the measurement of intraoperative blood loss.
Overall assessment	Good

Citation	O'Connor PJ, Hanson J, Finucane BT. Induced hypotension with epidural/general anesthesia reduces transfusion in radical prostate surgery. Can J Anesth 2006;53(9):873-880.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	Anaesthesiologists were not blinded, however, only 23% of the transfusions were decided by the anaesthesiologist. The remaining 77% of transfusions were initiated postoperatively by non-study personnel.
Overall assessment	Good.

Citation	Piper SN, Suttner SW, Maleck WH, Kumle B, Haisch G, Boldt J. Effects of sodium nitroprusside-induced controlled hypotension on pancreatic function assessed by pancreatitis-associated protein in patients undergoing radical prostatectomy. Eur J Anaesthesiol 2002;19(8):609-613.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NR	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	This study did not include a description of the blinding methods employed, if any. Also, as the primary aim of this study was not blood loss/transfusion, the authors did not discuss these outcomes in detail.
Overall assessment	Good.

Citation	Sood S, Jayalaxmi TS, Vijayaraghavan S, Nundy S. Use of sodium nitroprusside induced hypotensive anaesthesia for reducing blood loss in patients undergoing lienorenal shunts for portal hypertension. Br J 1987;74(11):1036-1038.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NR	B. Was the study double-blinded?
N	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	The study provides no assessment/discussion of possible limitations or bias. The final study sample size of 18 patients is small, however statistical significance was achieved in the analysis.
Overall assessment	Fair

Citation	Suttner SW, Piper SN, Lang K, Huttner I, Kumle B, Boldt J. Cerebral effects and blood sparing efficiency of sodium nitroprusside-induced hypotension alone and in combination with acute normovolaemic haemodilution. Br J Anaesth 2001;87(5):699-705.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	This RCT included a modest number of subjects, although initial power calculations suggest that the study was sufficiently powered. Information as to the method of randomising and blinding was not specified. The analyses performed were appropriate and the results presented clearly.
Overall assessment	Good

Intervention 6 – Prevention of hypothermia

Level I evidence

Citation	Mahoney CB, Odom J. Maintaining intraoperative normothermia: a meta-analysis of outcomes with costs (Structured abstract). AANA J 1999;67:155-164.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
N	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
N	F. Were the methods for pooling the data appropriate?
N	G. Were the sources of heterogeneity explored?
Comments	The inclusion of non-randomised trials (3/18) and the lack of information on the allocation method and blinding of individual studies diminish the quality of this study.
Overall assessment	Poor

Citation	Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. Anesthesiology 2008;108(1):71-77.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	F. Were the methods for pooling the data appropriate?
Y	G. Were the sources of heterogeneity explored?
Comments	Detailed characteristics of included studies were absent; quality scores were assigned for each study. The statistical analyses were well conducted and clearly presented. The presence of publication bias and study effect were also examined.
Overall assessment	Good

Citation	Scott EM, Buckland R. A systematic review of intraoperative warming to prevent postoperative complications (Structured abstract). AORN Journal 2006;83:1090-1104.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
N	F. Were the methods for pooling the data appropriate?
N	G. Were the sources of heterogeneity explored?
Comments	This review provides clear description of the randomisation, inclusion and exclusion criteria, and quality assessment of the included studies. However, the pooled estimates for morbid cardiac events were derived from just two studies, while the need for blood transfusion was derived from three studies. No assessment of heterogeneity or publication bias was performed.
Overall assessment	Fair

Level II evidence

Citation	Jeong SM, Hahm KD, Jeong YB, Yang HS, Choi IC. Warming of intravenous fluids prevents hypothermia during off-pump coronary artery bypass graft surgery. Journal of cardiothoracic and vascular anesthesia 2008;22:67-70.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	The authors recognise that the small sample size was likely underpowered to detect changes in clinical data, as the study was designed to be powered to detect a change in patient temperature. Investigators were not blinded the treatment group of the subjects, this may have led to bias.
Overall assessment	Poor.

Citation	Kim YS, Lee JY, Yang SC, Song JH, Koh HS, Park WK. Comparative Study of the Influence of Room-Temperature and Warmed Fluid Irrigation on Body Temperature in Arthroscopic Shoulder Surgery. Arthroscopy J Arthroscopic Relat Surg 2009;25(1):24-29.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	This RCT had clearly defined research questions and methods. It did not clearly describing the blinding or randomisation methods used. Based on the results of previous studies, their power calculation indicated that they had over 80% power.
Overall assessment	Fair

Citation	Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: A randomised controlled trial. Lancet 2001;358(9285):876-880.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NR	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	Prospective power calculations indicated that the sample size provided 90% power to detect a 5% change in infection rates. Statistical analyses performed were appropriate, with multivariate analysis used to identify possible risk factors.
Overall assessment	Good

Citation	Yau TM, Carson S, Weisel RD, Ivanov J, Sun Z, Yu R, Glynn MF, Teasdale SJ. The effect of warm heart surgery on postoperative bleeding. The Journal of thoracic and cardiovascular surgery 1992;103:1155-1162.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
N	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	Antifibrinolytic therapy was concurrently used by some patients in this study, and was not controlled for in this study; however, the use of such therapy had no bearing on the assignment to treatment group and as such would have had a non-differential effect, if any. The authors recognised that their sample size may have been underpowered to detect differences between treatment groups.
Overall assessment	Fair

Citation	Zhao J, Luo AL, Xu L, Huang YG. Forced-air warming and fluid warming minimize core hypothermia during abdominal surgery. Chinese medical sciences journal / Chinese Academy of Medical Sciences 2005;20:261-264.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	This RCT did not provide a description of the blinding or randomisation methods employed.
Overall assessment	Fair

Intervention 7 – Point-of-care testing using thromboelastography

Level II evidence

Citation	Ak, K., Isbir, SC., et al., Thromboblastography-based algorithm reduces blood product use after elective CABG: a prospective randomised study. J Card Surg 2009;24:404-410.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	Anaesthesiologist performing transfusion was blinded to the patient's group assignment.
Overall assessment	Fair

Citation	Avidan M.S., Alcock E.L. et al. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. British Journal of Anaesthesia. 2004; 2:176-86.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Royston D. and von Kier S. Reduced haemostatic factor transfusion using heparinise-modified thromboelastography during cardiopulmonary bypass. British Journal of Anaesthesia. 2001; 4:575-8.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Uncertain	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Poor

Citation	Shore-Lesserson L., Manspeizer H.E. et al. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesthesia and analgesia. 1999; 88:312-9.
Unclear	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	All staff appointed with caring for the patient directly were blinded.
Overall assessment	Fair

Citation	Westbrook AJ., Olsen J. et al. Protocol based on thrombolestaograph (TEG) out-performs physician preference using laboratory coagulation tests to guide blood replacement during and after cardiac surgery: a pilot study. Heart , Lung and Circulation.2009;18:277-288.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	Surgeons were blinded to the method of haemostasis.
Overall assessment	Fair

Level III evidence

Citation	Avidan M.S., Alcock E.L. et al. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. British Journal of Anaesthesia. 2004; 2:176-86.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Spalding, GJ., Hartrumpf, M. et al. Cost reduction of peri operative coagulation management in cardiac surgery: value of "bedside" thrombelastography (ROTEM). Eur J Cardiothorac Surg 2007;31:1052-1057.
Y	A. How were subjects selected for the 'new' intervention?
Y	B. How were subjects selected for the comparison or control group?
Y	C. Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the study design or analysis?
N	D. Was the measurement of outcomes unbiased (ie, blinded to treatment group and comparable across groups?)
N	E. Was follow-up long enough for outcomes to occur?
Y	F. Was follow-up complete and were there exclusions from analysis?
Comments	
Overall assessment	Fair

Intervention 8 – Administration of antifibrinolytics & DDAVP

Level I evidence

Citation	Abrishami A, Chung F, Wong J (2009) Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. Can J Anesth 56: 202-212.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Brown JR, Birkmeyer NJO, O'Connor GT (2007) Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation 115: 2801-2813.
N	A. Was a clinical question clearly defined?
N	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Medline search only conducted. Given the funnel plot indicated potential publication bias it may have been wise to expand the search to identify additional studies. No reporting of results of individual included studies. A number of data extraction errors were identified when checking one of the subgroup analyses.
Overall assessment	Fair

Citation	Carless PA, Stokes BJ, Moxey AJ, Henry DA (2004) Desmopressin use for minimising perioperative allogenic blood transfusion. Cochrane Database of Systematic Reviews. Issue 1. Article No.: CD001884. DOI: 10.1002/14651858.CD001884.pub2.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Included studies generally considered to be of poor methodological quality.
Overall assessment	Good

Citation	Crescenzi G, Landoni G, Biondi-Zoccai G et al (2008) Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. Anesthesiology 109: 1063-1076.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
N	Were the sources of heterogeneity explored?
Comments	Reasonable literature search and selection and extraction of data. No quality assessment undertaken so limited quality information available for individual studies. No exploration of reasons for heterogeneity carried out.
Overall assessment	Fair

Citation	Gurusamy KS, Sharma D, Davidson BR (2009) Pharmacological interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database of Systematic Reviews. 009,Issue 4.Art.No.: CD008085. DOI:10.1002/14651858. CD008085.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
NA	Were the methods for pooling the data appropriate?
NA	Were the sources of heterogeneity explored?
Comments	Comprehensive literature search carried out. Quality assessment undertaken. Single study only available for each comparison. Authors note all studies at high risk of bias.
Overall assessment	Good

Citation	Henry DA, Carless PA, Moxey AJ et al (2007) Antifibrinolytic use for minimising perioperative allogenic blood transfusion. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD001886. DOI: 10.1002/14651858.CD001886.pub2.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Comprehensive literature search carried out. Quality assessment undertaken. Subgroup analyses performed on *a priori* categories including surgery, transfusion protocol, dose and trial quality.
Overall assessment	Good

Citation	Henry DA, Carless PA, Fergusson D, et al (2009) The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ 180(2): 183-193.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Comprehensive literature search carried out. Some missing data on individual studies but the majority of these were provided in the Henry 2007 review.
Overall assessment	Good

Citation	Kagoma YK, Crowther MA, Douketis J et al (2009) Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopaedic surgery: a systematic review of randomized trials. Thrombosis Research 123: 687-696.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Included studies generally considered to be of good methodological quality.
Overall assessment	Good

Citation	*Systematic review:* Kongnyuy EJ, Wiysonge CS (2009) Interventions to reduce haemorrhage during myomectomy for fibroids. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD005335. DOI: 10.1002/14651858.CD005335.pub3. *Single included RCT:* Caglar GS, Tasci Y, Kayikcioglu F et al (2008) Intravenous tranexamic acid use in myomectomy: a prospective randomised double-blind placebo controlled study. European Journal of Obstetrics, Gynecology and Reproductive Biology 137(): 227-231.
Systematic review	
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
NA	Were the methods for pooling the data appropriate?
NA	Were the sources of heterogeneity explored?
Comments	Cochrane review; extensive literature search; quality assessment of included studies; appropriate analysis.
Overall assessment	Good
RCT	
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Computer generated randomisation code; treatments in sequentially numbered identical containers; patients, surgeons and anaesthetists blinded to treatment allocation; full follow-up of patients.
Overall assessment	Good

Citation	Liu C-M, Chen J, Wang X-H (2008) Requirements for liver transfusion and postoperative outcomes in orthotopic liver transplantation: a meta-analysis on aprotinin. World J Gatroenterol 14(9): 1425-1429.
Y	A. Was a clinical question clearly defined?
N	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results of the individual studies appropriately summarised?
N	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Inadequate search; included one non-RCT and one active-controlled RCT; no quality assessment; no details on individual studies provided.
Overall assessment	Poor

Citation	McIlroy DR, Myles PS, Phillips LE, Smith JA (2009) Antifibrinolytics in cardiac surgical patients receiving aspirin: a systematic review and meta-analysis.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Comprehensive literature search carried out. Quality assessment undertaken. Appropriate analysis methods used. Subgroup and sensitivity analyses undertaken.
Overall assessment	Good.

Citation	Schouten ES, van de Pol A, Schouten ANJ et al (2009) The effect of aprotinin, tranexamic acid and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. Pediatr Cri Care Med 10(2): 182-190.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	Comprehensive literature search carried out. Quality assessment undertaken. Not all individual results and pooled results provided. Meta-regression analysis carried out using potential confounders for the cardiac studies due to heterogeneity (age, weight and time on cardiopulmonary bypass).
Overall assessment	Fair.

Citation	Tzortzopoulou A, Cepeda MS, Schumann R et al (2008) Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD006883. DOI: 10.1002/14651858.pub2.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results of the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
N	Were the sources of heterogeneity explored?
Comments	Comprehensive literature search carried out. Quality assessment undertaken. 4/6 studies considered to have low risk of bias and 2/6 considered to have moderate risk of bias.
Overall assessment	Good

Level II evidence

Citation	Alvarez JC, Santiveri FX, Ramos I et al (2008) Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. Transfusion 48: 519-525.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Computer-generated stratified randomisation method used; sealed envelopes. Double-blind. 15 patients excluded from analysis following randomisation, more in treatment than control group.
Overall assessment	Fair

Citation	Apostolakis E, Panagopoulos N, Koletsis EN, Crockett J, Stamou-Kouki H, Sourgiadaki E, Filos K, Dougenis D (2008) Influence of ultra low dose aprotinin on thoracic surgical operations: a prospective randomized trial. Journal of Cardiothoracic Surgery 3:14.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomisation; single-blind – treating anaesthetist aware of treatment allocation so potential for bias; small trial.
Overall assessment	Fair

Citation	Athanasiadis T, Beule AG, Wormald PJ (2007) Effects of topical antifibrinolytics in endoscopic sinus surgery: a pilot randomized controlled trial. Am J Rhinol 21: 737-742.
Unclear	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	The method of randomisation was not reported. The anaesthetist prepared treatments so unclear if this could have resulted in unblinding. Outcome rating scales used not validated.
Overall assessment	Fair

Citation	Berenholtz SM, Pham JC, Garrett-Mayer E et al (2009) effect of epsilon aminocaproic acid on red-cell transfusion requirements in major spinal surgery. Spine 34(19): 2096-2103.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Computer-generated, stratified randomisation method used. Double-blind. All patients included in analysis. Study was underpowered to detect a 1-unit difference in total blood transfusion.
Overall assessment	Good.

Citation	Chen CC, Wang CC, Wang, CP et al (2008) Prospective, randomized, controlled trial of tranexamic acid in patients who undergo head and neck surgery. Otolaryngology – Head and Neck Surgery 138: 762-767.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Computer-generated stratified randomisation method used. Double-blind. 7 patients (8%) excluded from analysis following randomisation.
Overall assessment	Fair

Citation	Choi WS, Irwin MG, Samman N (2009) The effect of tranexamic acid on blood loss during orthognathic surgery: a randomized controlled trial. J Oral Maxillofac Sug 67: 125-133.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Computer-generated stratified randomisation method used/sealed envelopes. Double-blind. 12 patients (16%) excluded from analysis following randomisation.
Overall assessment	Fair

Citation	Colwell Jr CW, Chelly JE, Murkin JM, Stevens D, O'Keefe TJ, Hall R, Parvizi J (2007) Randomized study of aprotinin effect on transfusions and blood loss in primary THA. Clinical Orthopaedics and Related Research 465: 189-195.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised; double-blind; all patients included in analysis.
Overall assessment	Good

Citation	Elwatidy S, Jamjoon Z, Elgamal E et al (2008) Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. Spine 33(24): 2577-2580.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised using odd/even numbers so could be easily worked out; all subjects included in analysis.
Overall assessment	Fair

Citation	Fawzy H, Elmistekawy E, Bonneau D et al (2009) Can local application of tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. Journal of Cardiothoracic Surgery 4:25.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomisation using random number tables; double-blind; full follow-up of patients
Overall assessment	Good

Citation	Gharabaghian M, Eghtesadi-Araghi P (2006) The efficacy of epsilon-aminocaproic acid and its timing in reducing blood loss in major cardiac coronary bypass surgery: a randomized double-blinded placebo-controlled study. International journal of Pharmacology 2(1): 131-135.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Study was described as randomised but no details of method and concealment of allocation was provided. Not stated whether all patients included in the analysis although this was likely.
Overall assessment	Fair.

Citation	Grant MC, Kon Z, Joshi A, Christenson E, Kallam S, Burris N, Gu J, Poston RS (2008) Is aprotinin safe to use in a cohort at increased risk for thrombotic events: results from a randomized, prospective trial in off-pump coronary artery bypass. Ann Thorac Surg 86: 815-822.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
N	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Computer-generated randomisation; double-blind; no baseline details reported; some patients not included in analysis.
Overall assessment	Fair

Citation	Jabalami M, Zakeri K (2006) Evaluation of topical tranexamic acid on intraoperative bleeding in endoscopic sinus surgery. Iran J Med Sci 31(4): 221-223.
NR	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NR	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
NR	D. Were all randomised patients included in the analysis?
NR	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Poor reporting of randomisation, blinding, outcome assessment and follow-up
Overall assessment	Poor

Citation	Jimenez JJ, Iribarren JL, Lorente L et al (2007) Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized controlled trial. Critical care: 11 R117.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomisation using random number tables; double-blind; full follow-up of patients
Overall assessment	Good

Citation	Later AFL, Maas JJ, Engbers FHM et al (2009) Tranexamic acid and aprotinin in low- and intermediate risk cardiac surgery: a non-sponsored, double-blind, randomised placebo-controlled trial. European Journal of Cardiothoracic Surgery 36: 322-329.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomisation; double-blind; 9% of patients not included in analysis but reasonably large trial.
Overall assessment	Good

Citation	Leijdekkers VJ, Vahl AC, Mackaay AJC, Huijgens PC, Rauwerda JA (2006) Aprotinin does not diminish blood loss in elective operations for infrarenal abdominal aneurysms: a randomized, double-blind controlled trial. Ann Vasc Surg 20: 322-329.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised; described as double-blind but no details given; all patients included in analysis but very small trial.
Overall assessment	Fair

Citation	Maddali MM, Rajakumar MC (2007) Tranexamic acid and primary coronary artery bypass surgery: a prospective study. Asian Cardiovascular and Thoracic Annals 15: 313-319.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomisation; double-blind; all patients included in analysis.
Overall assessment	Good

Citation	Mayur G, Purvi P, Ashoo G, Panjak D (2007) Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section: a randomized case controlled prospective study. The Journal of Obstetrics and Gynecology of India 57(3): 227-230.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Unsecure method of randomisation, open-label.
Overall assessment	Fair

Citation	Mehr-Aein A, Sadeghi M, Madani-civi M (2007) Does tranexamic acid reduce blood loss in off-pump coronary artery bypass? Asian cardiovascular and Thoracic Annals 15: 285-289.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised, double-blind, all patients included in analysis.
Overall assessment	Good

Citation	Mehraien A, Ghafari A, Mohammadi SS (2009) Effect of topical aprotinin on early postoperative bleeding and ICU stay after coronary artery bypass graft surgeries. Pakistan Journal of Biological Sciences 12(10): 813-816.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised; double-blind; all patients included in analysis.
Overall assessment	Good

Citation	Nurözler F, Kutlu T, Küçük G (2008) Aprotinin for patients exposed to clopidogrel before off-pump coronary bypass. Asian Cardiovascular and Thoracic Annals 16: 483-487.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised; double-blind; all patients included in analysis; small study.
Overall assessment	Fair

Citation	Sadegi M, Mehr-Aein A (2007) Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A prospective randomised double-blind study in 67 patients. Acta Medica Iranica 45(6): 437-442.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised, double-blind, all patients included in analysis.
Overall assessment	Good

Citation	Sekhavat L, Tabatabah A, Dalili M et al (2009) Efficacy of tranexamic acid in reducing blood loss after cesarean section. The Journal of maternal-Fetal and Neonatal Medicine 22(1): 72-75.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	Unsecure method of randomisation, open-label.
Overall assessment	Poor

Citation	Taghaddomi RJ, Mirzaee A, Attar AS et al (2009) Tranexamic acid reduces blood loss in off-pump coronary artery bypass surgery. Journal of Cardiothoracic and Vascular Anaesthesia 23(3): 312-315.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised, double-blind, 7.4% of randomised patients not included in the analysis.
Overall assessment	Fair

Citation	Wong J, El Beheiry H, Rampersaud YR et al (2008) Tranexamic acid reduces perioperative blood loss in adult patients having spinal fusion surgery. Anesth Analg 107: 1479-1486.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Randomised, double-blind, 2.4% of randomised patients not included in the analysis.
Overall assessment	Good

Intervention 9 – Appropriate patient positioning

Level II evidence

Citation	De Sio M, Autorino R, Quarto G, Calabro F, Damiano R, Giugliano F, Mordente S, D'Armiento M. Modified Supine versus Prone Position in Percutaneous Nephrolithotomy for Renal Stones Treatable with a Single Percutaneous Access: A Prospective Randomized Trial. Eur Urol 2008;54(1):196-203.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	Not possible for surgeons to be blinded of intervention.
Overall assessment	Good.

Citation	Ko MT, Chuang KC, Su CY. Multiple analyses of factors related to intraoperative blood loss and the role of reverse Trendelenburg position in endoscopic sinus surgery. Laryngoscope 2008;118(9):1687-1691.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Not possible for surgeons to be blinded of intervention.
Overall assessment	Fair

Citation	Ong SM, Taylor GJSC. Can knee position save blood following total knee replacement? Knee 2003;10(1):81-85.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
NR	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Pace A, Yousef A. The effect of patient position on blood loss in primary cemented total hip arthroplasty. Arch Orthop Trauma Surg 2008;128(10):1209-1212.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Not possible to blind surgeon from patients' treatment group.
Overall assessment	Fair

Citation	Park CK. The effect of patient positioning on intraabdominal pressure and blood loss in spinal surgery. Anesth Analg 2000;91(3):552-557.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
Y	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
Y	F. Were any subgroup analyses carried out?
Comments	This study was well described. Appropriate statistical tests, such as the use of non-parametric tests were used, in light of the modest sample size (n=40).
Overall assessment	Good

Citation	Widman J, Isacson J. Lateral position reduces blood loss in hip replacement surgery: A prospective randomized study of 74 patients. Int Orthop 2001;25(4):226-227.
Y	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
N	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	Not possible for the surgeon to be blinded to the treatment group of the patient.
Overall assessment	Fair.

Intervention 10 – Preoperative autologous donation

Level I evidence

Citation	Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine 14:123-144.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, and McCollum C. (2006) Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model (Provisional abstract). Health Technology Assessment 10:1-228.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Duffy G and Neal KR. (1996) Differences in postoperative infection rates between patients receiving autologous and allogeneic blood transfusion: a meta-analysis of published randomized and nonrandomized studies (Structured abstract). Transfusion Medicine 6:325-328.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
NA	Were the methods for pooling the data appropriate?
NA	Were the sources of heterogeneity explored?
Comments	Limited trial information provided
Overall assessment	Fair

Citation	Forgie MA, Wells PS, Laupacis A, and Fergusson D. (1998) Preoperative autologous donation decreases allogeneic transfusion but increases exposure to all red blood cell transfusion: Results of a meta- analysis. Archives of Internal Medicine 158:610-616.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Gurusamy KS, Li J, Sharma D, and Davidson BR. (2009) Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database of Systematic Reviews: Reviews 2009. Issue. 4
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Henry DA, Carless PA, Moxey AJ, O'Connell D, Forgie MA, Wells P, and Fergusson DA. (2001) Preoperative autologous donation for minimising perioperative allogeneic blood transfusion. Cochrane Database of Systematic Reviews 2001; Issue 4
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
Y	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
Y	Were the sources of heterogeneity explored?
Comments	
Overall assessment	Good

Citation	Laupacis A and Fergusson D. (1998) The efficacy of technologies to minimise perioperative allogeneic transfusion (Structured abstract). Kluwer. Academic Publishers.17-36.
Y	A. Was a clinical question clearly defined?
Y	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
Y	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
N	Were the sources of heterogeneity explored?
Comments	Baseline characteristics not reported
Overall assessment	Fair

Citation	Vamvakas EC. (2002) Meta-analysis of randomized controlled trials investigating the risk of postoperative infection in association with white blood cell-containing allogeneic blood transfusion: The effects of the type of transfused red blood cell product and surgical setting. Transfusion Medicine Reviews 16:304-314.
Y	A. Was a clinical question clearly defined?
NR	B. Was an adequate search strategy used?
Y	C. Were the inclusion criteria appropriate and applied in an unbiased way?
N	D. Was a quality assessment of included studies undertaken?
N	E. Were the characteristics and results if the individual studies appropriately summarised?
Y	Were the methods for pooling the data appropriate?
N	Were the sources of heterogeneity explored?
Comments	No reporting of transfusion protocol, allocation concealment, blinding, ITT analysis.
Overall assessment	Poor

Level II evidence

Citation	Bouchard D, Marcheix B, Al Shamary S, Vanden Eynden F, Demers P, Robitaille D, Pellerin M, Perrault LP, and Carrier M. (2008) Preoperative autologous blood donation reduces the need for allogeneic blood products: A prospective randomized study. Canadian Journal of Surgery 51:422-427.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
Y	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
N	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	Fair

Citation	Hashimoto T, Kokudo N, Orii R, Seyama Y, Sano K, Imamura H, Sugawara Y, Hasegawa K, and Makuuchi M. (2007) Intraoperative blood salvage during liver resection: A randomized controlled trial. Annals of Surgery 245:686-691.
N	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
N	B. Was the study double-blinded?
Y	C. Were patient characteristics and demographics similar between treatment arms at baseline?
N	D. Were all randomised patients included in the analysis?
Y	E. Were the statistical methods appropriate?
NA	F. Were any subgroup analyses carried out?
Comments	No transfusion protocol was used
Overall assessment	Poor

Appendix F: Evidence summaries

Intervention 1 – Acute normovolemic haemodilution

Level I evidence

<table>
<tr><td colspan="5">Citation</td></tr>
<tr><td colspan="5">Bryson GL, Laupacis A, and Wells GA. (1998) Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. Anesthesia and Analgesia 86:9-15.</td></tr>
<tr><td colspan="5">Affiliation/Source of funds</td></tr>
<tr><td colspan="5">None declared</td></tr>
<tr><td colspan="2">Study design</td><td colspan="2">Level of evidence</td><td>Location/setting</td></tr>
<tr><td colspan="2">SR
Search conducted August 1996</td><td colspan="2">I</td><td>NA</td></tr>
<tr><td colspan="3">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="3">Intraoperative ANH: only those trials in which whole blood was withdrawn on the day of surgery and replaced with a crystalloid or colloid solution were considered to represent ANH.</td><td colspan="2">Control group</td></tr>
<tr><td colspan="5">Population characteristics</td></tr>
<tr><td colspan="5">Any patients undergoing a surgical procedure.</td></tr>
<tr><td colspan="3">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="3">NR</td><td colspan="2">Proportion of patients transfused with at least 1 unit of allogeneic blood in the perioperative period, volume of allogeneic blood transfused, volume of blood withdrawn during haemodilution, discharge haematocrit.</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation</td><td>Results</td><td>Blinding analysis</td><td>Treatment/measurement bias</td><td>Follow-up (ITT)</td></tr>
<tr><td>All trials were randomised (pseudorandom trials were excluded).
The median Jadad score was 1 of a possible 5. Only five trials, all scoring 2, exceeded the median.</td><td>SR did not report baseline characteristics.</td><td></td><td>Fifteen trials did not specify a transfusion protocol or used a protocol that set different transfusion thresholds in the ANH and control groups.</td><td>NR</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive)</td></tr>
<tr><td colspan="5">Good</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Outcome	Intervention group	Comparator group	Statistical significance
Mean volume of blood reserved, mL 24 trials (n=629; 629 ANH)	936		NA
Mean perioperative blood loss, mL 24 trials (n=1218; 629 ANH, 589 control)	1268	1348	NR
Patients exposed to at least 1 unit of allogeneic blood 16 trials (n=615; 308 ANH, 307 control)			OR (95% CI): 0.31 (0.15, 0.62) P<0.05 (P*het=0.013)* ANH improves outcome
Patients exposed to at least 1 unit of allogeneic blood (cardiac surgery) 6 trials (n=266; 128 ANH, 138 control)			OR (95% CI): 0.51 (0.26, 0.99) P<0.05 (P*het*=0.945) ANH improves outcome
Patients exposed to at least 1 unit of allogeneic blood (orthopaedic surgery) 3 trials (n=174; 88 ANH, 86 control)			OR (95% CI): 1.00 (0.01, 4.47) P>0.05 (P*het*=0.032) ANH worsens outcome
Patients exposed to at least 1 unit of allogeneic blood (miscellaneous surgery) 7 trials (n=175; 92 ANH, 83 control)			OR (95% CI): 0.05 (0.01, 0.18) P<0.05 (P*het*=0.226) ANH improves outcome
Patients exposed to at least 1 unit of allogeneic blood (<1000 mL of blood withdrawn preoperatively in ANH group)			OR (95% CI): 0.43 (0.18, 1.02) P>0.05 (P*het*=NR) No significant difference
Patients exposed to at least 1 unit of allogeneic blood (≥1000 mL of blood withdrawn preoperatively in ANH group)			OR (95% CI): 0.16 (0.04, 0.65) P<0.05 (P*het*=NR) ANH improves outcome
Patients exposed to at least 1 unit of allogeneic blood (transfusion protocol)			OR (95% CI): 0.64 (0.31, 1.31) P>0.05 (P*het*=NR) No significant difference
Patients exposed to at least 1 unit of allogeneic blood (no transfusion protocol)			OR (95% CI): 0.12 (0.04, 0.37) P<0.05 (P*het*=NR) ANH improves outcome
Units of allogeneic blood transfused 13 trials (n=568; 299 ANH, 269 control)			WMD (95% CI): -2.22 (-3.57, -0.86) P<0.05 (P*het*<0.001) ANH improves outcome

Units of allogeneic blood transfused (cardiac surgery) 6 trials (n=365; 197 ANH, 168 control)			WMD (95% CI): -2.83 (-5.34, -0.31) P<0.05 (P*het<0.001*) ANH improves outcome
Units of allogeneic blood transfused (orthopaedic surgery) 2 trials (n=60; 30 ANH, 30 control)			WMD (95% CI): -1.54 (-4.41, 1.32) P>0.05 (P*het*<0.001) No significant difference
Units of allogeneic blood transfused (miscellaneous surgery) 5 trials (n=143; 72 ANH, 71 control)			WMD (95% CI): -2.26 (-3.71, -0.80) P<0.05 (P*het*=0.004) ANH improves outcome
Units of allogeneic blood transfused (<1000 mL of blood withdrawn preoperatively in ANH group)			WMD (95% CI): -2.30 (-3.79, -0.81) P<0.05 (P*het*=NR) ANH improves outcome
Units of allogeneic blood transfused (≥1000 mL of blood withdrawn preoperatively in ANH group)			WMD (95% CI): -1.69 (-3.42, -0.03) P<0.05 (P*het*=NR) ANH improves outcome
Units of allogeneic blood transfused (transfusion protocol)			WMD (95% CI): 0.25 (-0.60, 0.10) P>0.05 (P*het*=NR) No significant difference
Units of allogeneic blood transfused (no transfusion protocol)			WMD (95% CI): -3.01 (-3.47, -2.55) P<0.05 (P*het*=NR) AMH improves outcome
Difference in perioperative blood loss, mL 13 trials (n=500; 245 ANH, 255 control)			WMD (95% CI): -117 (-292, 58) P>0.05 (P*het*<0.001) No significant difference
Difference in perioperative blood loss (cardiac surgery), mL 7 trials (n=350; 169 ANH, 181 control)			WMD (95% CI): -233 (-459, -5) P<0.05 (P*het*<0.001) ANH had less perioperative blood
Difference in perioperative blood loss (orthopaedic surgery), mL 1 trial (n=31; 16 ANH, 15 control)			WMD (95% CI): 33 (-512, 578) P>0.05 (P*het*=NA) No significant difference

Difference in perioperative blood loss (miscellaneous surgery), mL 5 trials (n =119; 60 ANH, 59 control)			WMD (95% CI): -97 (-339, 145) P>0.05 (P*het*=0.013) No significant difference
Mortality 6 trials (n=170)			OR (95% CI): 0.67 (0.14, 3.20)
Myocardial infarction 2 trials (n=40)			OR (95% CI): 1.00 (0.06, 17.07)
DVP 2 trials (n=123)			OR (95% CI): 0.67 (0.14, 3.20)
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population			
Applicability			
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).			
Comments			

Abbreviations: ANH, acute normovolemic haemodilution; NA, not applicable; NR, not reported; SR, systematic review.

Citation				
Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine 14:123-144.				
Affiliation/Source of funds				
The research was supported by a grant obtained from the National Health and Medical Research Council of Australia and a special purpose grant from the Hunter Area Pathology Service, Australia.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs and observational studies with meta-analysis Search conducted July 2002	I	NA		
Intervention	Comparator			
Autologous transfusion techniques: preoperative Autologous blood deposit (PAD), ANH, and cell salvage. NOTE: This form only contains RCT info relevant for ANH. Sample size n=704	Comparator: no Autologous transfusion technique (active versus active comparisons were excluded). Sample size n=591			
Population characteristics				
Patients older than 18 years undergoing any type of surgery. The mean age of participants in ANH trials was 56 years. The trials included more than twice as many males as females (2.3:1). Twelve trials involved cardiac surgery, seven involved orthopaedic surgery, and 11 involved various other operative procedures (eg, urological, thoracic, or vascular).				
Length of follow-up	Outcomes measured			
NA	Mortality, re-operation, infection, wound complication, thrombosis, non-fatal MI, rate of allogeneic red blood cell transfusion, and volume of allogeneic blood transfused.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation concealment and the method of randomisation were judged by the SR authors to be inadequate in 100 and 92% of trials respectively (kappa=0.78-1.0).	SR did not discuss similarity between preoperative data and baseline characteristics for the intervention groups.	The majority (96%) of the included RCTs assessing ANH were unblended.	Not detected	NR
Overall quality assessment (descriptive)				
Fair				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Mortality 8 trials (n=NR)	NR	NR	RR (95% CI): 1.16 (0.19, 7.15) P*het*=NR
Morbidity: infection 2 trials (n=NR)	NR	NR	RR (95% CI): 4.94 (0.61, 40.19) P*het*=NR
Morbidity: thrombosis 3 trials (n=NR)	NR	NR	RR (95% CI): 0.44 (0.21, 0.93) P*het*=NR
Morbidity: non-fatal MI 3 trials (n=NR)	NR	NR	RR (95% CI): 3.43 (0.15, 79.74) P*het*=NR
Re-operation 7 trials (n=NR)	NR	NR	RR (95% CI):1.59 (0.20, 12.53) P*het*=NR
Rate of allogeneic blood transfusion: all studies 25 trials (n=1081; 567 ANH, 514 control)	273/567 (48%)	357/514 (69%)	RR (95% CI): (P*het*<0.00001)
Rate of allogeneic blood transfusion: cardiac surgery 10 trials (n=NR)	NR	NR	RR (95% CI): 0.77 (0.57, 1.04)
Rate of allogeneic blood transfusion: orthopaedic surgery 6 trials (n=NR)	NR	NR	RR (95% CI): 0.79 (0.60, 1.06)
Rate of allogeneic blood transfusion: miscellaneous surgery 9 trials (n=NR)	NR	NR	RR (95% CI): 0.42 (0.24, 0.74)
Rate of allogeneic blood transfusion: transfusion protocol used 16 trials (n=NR)	NR	NR	RR (95% CI): 0.81 (0.62, 1.00)
Rate of allogeneic blood transfusion: transfusion protocol not used/reported 9 trials (n=NR)	NR	NR	RR (95% CI): 0.53 (0.36, 0.76)
Difference in units of allogeneic blood transfused 17 trials	NR	NR	WMD (95% CI) Overall: -1.9 (-1.1, -2.7) Studies with a transfusion protocol: -1.0 (-1.7, -0.4) Studies without a transfusion protocol: -3.0 (-4.9, -1.1)
Hospital length of stay, d 3 trials (N=96)	NR	NR	WMD (95% CI): 0.21 (-1.26, 1.68)

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
Patients considered similar to guideline target population	
Applicability	
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).	
Comments	

Abbreviations: ANH, acute normovolemic haemodilution; MI, myocardial infarction; PAD, preoperative autologous donation; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; WMD, weighted mean difference.

Citation				
Gurusamy KS, Li J, Sharma D, and Davidson BR. (2009) Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database of Systematic Reviews 2009; Issue. 4				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR of RCTs Search conducted November 2008	I	NA		
Intervention	Comparator			
Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection: low central venous pressure, PAD, ANH, ANH with controlled hypotension, and hypoventilation. NOTE: This form only contains info relevant for ANH.[1] n=115	Standard care n=118			
Population characteristics				
Patients undergoing liver resection. Trials were included irrespective of whether they included major or minor liver resections, normal or cirrhotic livers, vascular occlusion was used or not, and irrespective of the reason for liver resection.				
Length of follow-up	Outcomes measured			
NR	Perioperative mortality, perioperative morbidity, transfusion frequency, operating time, operative blood loss.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
All three trials had randomised allocation but unclear allocation concealment.	The authors of the SR stated that it was unclear whether any of the three trials were free of baseline imbalance.	None of the three trials blinded all outcomes.	The authors of the SR classified all of the trials as not being free of selective reporting as important outcomes, such as liver failure, were not reported.	Analysis performed with ITT.
Overall quality assessment (descriptive)				
Good				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Perioperative mortality 2 trials (n=150; 73 ANH, 77 control)			RR (95% CI): 0.35 (0.04, 3.32) P>0.05 (P*het*=1.00) No significant difference	
Perioperative morbidity: bile leak 1 trial (n=78; 39 ANH, 39 control)			RR (95% CI): 1.5 (0.27, 8.49) P>0.05 (P*het*=NA)	

Perioperative morbidity: intra-abdominal bleeding 2 trials (n=208; 102 ANH, 106 control)			RR (95% CI): 1.87 (0.4, 8.67) P>0.05 (P*het*=0.39)
Perioperative morbidity: intra-abdominal infection 1 trial (n=78; 39 ANH, 39 control)			RR (95% CI): 0.33 (0.04, 3.07) P>0.05 (P*het*=NA)
Perioperative morbidity: intra-abdominal collection requiring drainage 1 trial (n=130; 63 ANH, 67 control)			RR (95% CI): 1.26 (0.061, 2.60) P>0.05 (P*het*=NA)
Perioperative morbidity: wound infection 2 trials (n=208; 102 ANH, 106 control)			RR (95% CI): 0.84 (0.34, 2.03) P>0.05 (P*het*=0.18)
Perioperative morbidity: chest infection 1 trial (n=78; 39 ANH, 39 control)			RR (95% CI): 1.50 (0.27, 8.49) P>0.05 (P*het*=NA)
Number requiring allogeneic blood transfusion 3 trials (n=233; 115 ANH, 118 control)			RR (95% CI): 0.41 (0.25, 0.66) P<0.05 (P*het*=0.70) ANH improves outcome
Red cell transfusion 2 trials (n=150; 73 ANH, 77 control)			Mean difference (95% CI): -0.09 (-0.48, 0.29) P>0.05 (P*het*<0.00001) No significant difference
Operating time in minutes 2 trials (n=208; 102 ANH, 106 control)			Mean difference (95% CI): -28.86 (-57.37, -0.35) P<0.05 (P*het=0.90)* ANH improves outcome
Operative blood loss, mL 2 trials (n=98; 49 ANH, 49 control)			Mean difference (95% CI): 1.53 (-102.37, 105.44) P>0.05 (P*het*=0.83) ANH improves outcome
Length of hospital stay, days 1 trial (n=130; 63 ANH, 67 control)			Mean difference (95% CI): 0.0 (-2.66, 2.66) P>0.05 (P*het*=NA) No significant difference
Outcome	Clinical importance	Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Limited: the SR only included papers assessing ANH for liver resection, not other surgery types.			

Applicability
Of the three RCTs included in this SR, one was conducted in America, one in Israel, and the other was conducted in China. These countries have some differences to Aus/NZ health systems.
Comments

[1] The SR assesses both haemodilution versus control and haemodilution with bovine haemoglobin (HBOC-201) versus haemodilution with hydroxyl ethyl starch. This extraction form only includes data for haemodilution versus control.
Abbreviations: ANH; acute normovolemic haemodilution; M-H, Mantel-Haenszel estimate; NA, not applicable; NR, not reported; PAD, preoperative autologous donation; RCT, randomised controlled trial; RR, risk ratio; SR, systematic review.

Citation				
Laupacis A and Fergusson D. (1998) The efficacy of technologies to minimise perioperative allogeneic transfusion (Structured abstract). Kluwer. Academic Publishers.17-36.				
Affiliation/Source of funds				
NR				
Study design	Level of evidence	Location/setting		
SR Search conducted March 1997	I	NA		
Intervention	Comparator			
Technologies to minimise perioperative allogeneic transfusion: aprotinin, desmopressin, tranexamic acid, epsilon aminocaproic acid, erythropoietin, PAD, ANH. NB: this form only reports results for ANH.	Any			
Population characteristics				
Adult patients undergoing elective surgery. Types of surgery included cardiac, colorectal, liver resection and orthopaedic surgery.				
Length of follow-up	Outcomes measured			
NR	Proportion of patients receiving at least one unit of allogeneic packed red blood cells, perioperative MI, re-operations because of bleeding.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
NR	Baseline characteristics NR	NR	Use of transfusion protocol NR	NR
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Patients transfused with allogeneic blood			OR (95% CI): 0.31 (0.15, 0.62) "The likelihood was reduced in cardiac and miscellaneous procedures but not in orthopaedic surgery.
Patients transfused with allogeneic blood: <1000 mL blood withdrawn			OR (95% CI): 0.43 (0.18, 1.02)
Patients transfused with allogeneic blood: >1000 mL blood withdrawn			OR (95% CI): 0.16 (0.04, 0.65)

Outcome	Clinical importance	Clinical relevance
Patients transfused with allogeneic blood	1	1
Patients transfused with allogeneic blood: <1000 mL blood withdrawn	4	1
Patients transfused with allogeneic blood: >1000 mL blood withdrawn	1	1
EXTERNAL VALIDITY		
Generalisability		
The SR is generalisable for elective, non urgent surgery.		
Applicability		
The studies were mostly from countries with similar health-care systems to Australia		
Comments		

Abbreviations: ANH, acute normovolemic haemodilution; MI, myocardial infarction; NA, not applicable; NR, not reported; OR, odds ratio; PAD, preoperative autologous deposit; SR, systematic review.

Citation				
Segal JB, Blasco-Colmenares E, Norris EJ, and Guallar E. (2004) Preoperative acute normovolemic hemodilution: A meta-analysis. Transfusion 44:632-644.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR Search conducted October 2002	I	NA		
Intervention	Comparator			
ANH	Comparison group that did not receive ANH.			
Population characteristics				
Patients undergoing any surgery type				
Length of follow-up	Outcomes measured			
NR	Number of subjects who received allogeneic blood transfusion in the perioperative period, average amount of allogeneic blood received per patient in each study group, average volume of blood loss perioperatively, adverse events.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Of the 42 included studies, only 12 studies reported that the outcomes assessor was masked as to treatment assignment. Although all studies were randomised only 14 of the studies provided any description of the randomisation procedure.	SR did not report baseline characteristics	The patients were masked to treatment assignment in only four studies.	More than three-fourths of the studies reported the threshold at which transfusion was initiated.	NR
Overall quality assessment (descriptive)				
Fair				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Proportion receiving allogeneic blood perioperatively (ANH vs standard care) 25 trials (n=1409; 703 ANH, 706 standard care)			RR (95% CI): 0.96 (0.90, 1.01) P>0.05 (P*het*=0.98) No significant difference
Proportion receiving allogeneic blood perioperatively (trials with concurrent use of other blood conservation methods in both arms) 10 trials (n=NR)			RR (95% CI): 0.98 (0.91, 1.07) P>0.05 (P*het*=NA) No significant difference
Volume of allogeneic blood transfused intraoperatively (ANH vs standard care), mL[1] Number of trials not reported			WMD (95% CI): -303 (-555, -55) p<0.05 (P*het*<0.001) ANH improves outcome
Volume of allogeneic blood transfused intra- and postoperatively (ANH vs standard care), mL[2] 13 trials (n=735; 406 ANH, 329 standard care)			WMD (95% CI): -201 (-309, -92) P<0.05 (P*het*<0.001) ANH improves outcome
Volume of intraoperative blood loss (ANH vs standard care), mL Number of trials not reported			Pooled average difference (95% CI): 15 (-27, 58) P>0.05 (P*het*=0.26) No significant difference
Volume of intra- and postoperative blood loss (ANH vs standard care), mL 20 trials (n=1138; 565 ANH, 573 standard care)			WMD (95% CI): -91 (-157, -25) P<0.05 (P*het*<0.0001)
Mortality 17 trials (n=1191)	6/607 (1%)	10/584 (2%)	NR
Morbidity	Myocardial infarction: 7/502 (1%) Cardiac ischemia: 8/140 (6%) Left ventricular dysfunction: 2/133 (2%) Venous thromboembolism: 3/180 (2%) Cerebral infarction: 3/323 (1%) Hypotension during haemodilution: 2/234 (1%) Transfusion reaction: 0/131 (0%)	Myocardial infarction: 9/480 (2%) Cardiac ischemia: 9/137 (7%) Left ventricular dysfunction: 7/110 (6%) Venous thromboembolism: 2/180 (1%) Cerebral infarction: 2/343 (1%) Hypotension during haemodilution: 0/243 (0%) Transfusion reaction: 0/153 (0%)	NR

Outcome	Clinical importance	Clinical relevance
EXTERNAL VALIDITY		
Generalisability		
Patients considered similar to guideline target population		
Applicability		
Study performed in UK which has many similarities with the Aus/NZ healthcare systems.		
Comments		
NB: in this review units of blood were transformed to millilitres by assuming that 1 unit of whole blood contained 450 mL of blood and that 1 unit of RBCs had a volume of 300 mL.		

[1]The one trial that was an extreme outlier in the volume of blood transfused (Lilleaasen 1977) was removed from these analyses. The two studies that used the largest volume haemodilution (mean of 1500 mL of blood withdrawn) reduced the volume of intraoperative allogeneic transfusion most extremely (weighted mean difference, -720 mL; 95% CI: -475, -982).
[2]Trials using higher Hct levels to trigger transfusion demonstrated greater savings with ANH (P<0.001), as did older trials (P=0.04). There is also little difference between the large-volume and lower-volume studies (P=0.6).
Abbreviations: ANH, acute normovolemic haemodilution; NA, not applicable; NR, not reported; RR, risk ratio; SR, systematic review; WMD, weighted mean difference.

Level II evidence

Citation				
Akhlagh SH, Chohedri AH, Bazojoo A, and Nemati MH. (2007) A comparison of total amount of blood needed in patients taking autologous or homologous blood transfusion in coronary artery bypass grafting: A clinical randomized case-control trial. Pakistan Journal of Medical Sciences 23:542-545.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	Iran		
Intervention	Comparator			
ANH and retransfusion of autologous blood after separating the patient from the cardiopulmonary machine. n=30?[1]	Control: no withdrawal of blood and only allogeneic blood transfused. n=30?[1]			
Population characteristics				
Patients undergoing coronary artery bypass grafting (on-pump). Eighty percent of patients were male.				
Length of follow-up	Outcomes measured			
24 hours				
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is unclear whether allocation was concealed from those responsible for recruiting subjects.	The baseline characteristics of the treatment arms were matched.	All data were registered by an independent investigator	No transfusion protocol was reported.	There was no reported loss to follow-up
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Mean (SD) 24 h post-operational haematocrit concentration, %	36.5 (1.5)	37 (2)	P=0.21	
Mean total volume of blood transfused, mL	1815[2]	2010	P=0.024	
Clinical importance		Clinical relevance		
EXTERNAL VALIDITY				
Generalisability				
The study population is consistent with the guideline population.				

Applicability
The study was conducted in Iran, which may limit its applicability to the Australian context.
Comments

[1]Although the paper reports the total study population (n=60), it does not specify the number of patients randomised to each arm. The values of 30 patients for each arm is based on the assumption that the participants were evenly split between active and control treatments.
[2]Of the 1815 mL blood needed in the ANH group, 870 mL (47.9%) was homologous and 945 mL (52.1%) was autologous.

Citation				
Bennett J, Haynes S, Torella F, Grainger H, and McCollum C. (2006) Acute normovolemic hemodilution in moderate blood loss surgery: A randomized controlled trial. Transfusion 46:1097-1103.				
Affiliation/Source of funds				
NR				
Study design	Level of evidence		Location/setting	
RCT	II		UK hospital	
Intervention		Comparator		
ANH: autologous blood was collected immediately before surgery, aiming to reduce haemoglobin concentration to a target of 110 g per L. ANH blood was collected into 450 mL bags containing 63 mL of citrate-based anticoagulant; crystalloids were infused simultaneously to maintain normovolaemia. All autologous blood was returned within 6 hours of collection, starting on wound closure or sooner if a transfusion trigger was reached. If further transfusion was indicated, allogeneic blood was administered. n=78		Standard care: autologous transfusion was not offered. Allogeneic blood was transfused if a transfusion trigger was reached. The trigger for both intervention and comparator groups was based on a haemoglobin level of less than 80 g per L. n=77		
Population characteristics				
Patients undergoing elective hip surgery (anticipated blood loss between 1 to 1.5 L). Most patients underwent primary total hip replacement, with 15 revision hip arthroplasties (7 in ANH and 8 in standard transfusion) and 1 hip resurfacing procedure.				
Length of follow-up		Outcomes measured		
Unclear (at least until hospital discharge)		Proportion of patients requiring allogeneic transfusion and the volume of allogeneic blood transfused, postoperative complications (infective complications and hospital inpatient stay)		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised allocation. Unclear whether allocation to treatment groups was concealed from those responsible for recruiting subjects.	Twenty patients in each group were on anti-PLT, or anticoagulant drugs at the time of surgery; 29 in standard transfusion and 29 in ANH were on NSAIDs. There were no differences in preoperative Hb or PLT count.	Neither the anaesthetist nor the s surgical team could be blinded but patients were not told the allocated treatment.	Five patients, 1 in standard transfusion and 4 in ANH received allogeneic blood in violation of the trial protocol (2 units each) despite failing to reach any transfusion triggers. If these 5 patients had been excluded, the difference in transfused volumes (61 units vs 25 units) would have been significant (P=0.04)	All analysis follows ITT.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	

Mortality	1/78 (1.3%)	0/77 (0%)	P=0.50
Patients with at least one significant postoperative complication.	14/78 (18%)	30/77 (38%)	P=0.006
Morbidity	Cardiovascular event: 1/78 (1%) Postoperative infection: 7/78 (9%) Wound (non-infective): 2/78 (3%) Bleeding: 0/78 (0%) Venous thromboembolism: 2/78 (3%) Urinary retention: 3/78 (4%) Transfusion reaction: 0/78 (0%)	Cardiovascular event: 4/77 (5%) Postoperative infection: 17/77 (22%) Wound (non-infective): 0/77 (0%) Bleeding: 1/77 (1%) Venous thromboembolism: 1/77 (1%) Urinary retention: 3/77 (4%) Transfusion reaction: 1/77 (1%)	P-value Cardiovascular event: 0.21 Postoperative infection: 0.03 Wound (non-infective): 0.30 Bleeding: 0.49 Venous thromboembolism: 0.58 Urinary retention: 0.99 Transfusion reaction: 0.49
Patients requiring allogeneic transfusion	15 /78(19%)	22/77 (29%)	P=0.18
Units of allogeneic blood transfused	33	63	P=0.1
Median (IQR) postoperative hospital stay	7 (6, 9)	8 (6, 11)	P=0.03
Median (IQR) intraoperative blood loss (mL)	692 (452, 1019)	641 (477, 1007)	P=0.82
Median (IQR) total blood loss (mL)	1182 (840, 1646)	1210 (816, 1545)	P=0.82
Patients who needed to seek medical attention after discharge (either via their GP or local hospital)	29/78 (37%)	43/77 (56%)	P=0.02
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population			
Applicability			
Study performed in UK which has many similarities with the Aus/NZ healthcare systems.			
Comments			

Abbreviations: ANH, acute normovolemic haemodilution; Hb, haemoglobin; IQR, inter-quartile range; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PLT, platelet; RCT, randomised controlled trial.

Citation				
Casati V, Speziali G, D'Alessandro C, Cianchi C, Antonietta Grasso M, Spagnolo S, and Sandrelli L. (2002) Intraoperative low-volume acute normovolemic hemodilution in adult open-heart surgery. Anesthesiology 97:367-373.				
Affiliation/Source of funds				
NR				
Study design	Level of evidence		Location/setting	
RCT	II		Italy, hospital	
Intervention		Comparator		
Low volume ANH: 5-8 mL/kg of blood withdrawn before systemic heparinisation and replaced with colloid solutions. n=103		Standard care: no haemodilution n=101		
Population characteristics				
Patients undergoing on-CPB cardiac surgery. Preoperative exclusion criteria: age < 18 years, LVEF < 30%, preoperative haematocrit < 36% or haemoglobin less than 12 g/dl, history of haematologic diseases, chronic renal insufficiency (plasma creatinine > 2 mg/dl), and history of hepatic diseases.				
Length of follow-up		Outcomes measured		
Samples for evaluation of haemoglobin, haematocrit, platelet count, prothrombin time, activated partial thromboplastin time, creatinine, creatine phosphokinase, and creatine phosphokinase myocardial band isoenzyme were performed before the induction of anaesthesia (time 1), on arrival in ICU (time 2), 24 h after the arrival in ICU (time 3), 48 h after surgery (time 4), and at discharge (time 5). Blood loss was recorded during the first 24 h.		Transfusion frequency, amount of allogeneic blood transfused, amount of postoperative bleeding, postoperative complications, and postoperative haematochemical data.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was randomised using a computer-generated random number sequence. It is unclear whether allocation to treatment groups was concealed from those responsible for recruiting subjects.	Treatment groups had similar patient demographics, haematochemical levels. The intervention/control split for the entire set of cardiac operations assessed was close to even. Only the amounts of colloids and crystalloids infused before CPB, greater in ANH group, were significantly different.	Neither the patients nor the surgical staff/assessors were blinded to treatment allocation.	Not detected.	Study used per protocol analysis

Overall quality assessment (descriptive)			
Poor			
RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance[1]
Postoperative deaths[2]	4/103 (3.9%)	4/101 (4%)	P=0.98
Morbidity	Myocardial infarction: 2/103 (2%) renal failure: 3/103 (2.9%) minor neurological complications: 7/103 (6.9%) stroke: 2/103 (2%) pulmonary embolism: 0/103 (0%)	Myocardial infarction: 1/101 (1%) renal failure: 4/101 (4%) minor neurological complications: 8/101 (8%) stroke: 1/101 (1%) pulmonary embolism: 1/101 (1%)	P-value Myocardial infarction: P=0.58 renal failure: 0.68 minor neurological complications: 0.86 stroke: 0.58 pulmonary embolism: 0.49
Total number of patients transfused with allogeneic blood (including PRBC, FFP, and PLTC)	35/103 (34%)	36/101 (36%)	P=0.88
Units of allogeneic PRBC transfused / patients transfused	123/32	126/34	P=0.47
Median (IQR) bleeding 0-4 h (mL)	158 (106, 305)	172 (117.5, 265)	P=0.93
Median (IQR) total bleeding	374 (255, 704)	412 (313, 552)	P=0.94
Median (IQR) postoperative hospital stay (days)	7 (6, 9)	7 (6, 8.25)	P=0.54
Median (IQR) ICU stay (days)	1 (1, 1)	1 (1, 2)	P=0.49
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population.			
Applicability			
RCT performed in Italy; however the results should be applicable to the Australian setting.			
Comments			
Two patients (1 per group) did not complete the study: they died during the first 24 h postoperatively after cardiogenic shock refractory to maximal pharmacologic support and intra-aortic counter pulsation. They were excluded by statistical analysis. 202 patients entered in the statistical analysis.			

[1]The authors of the study conducted all statistical tests with per protocol analysis.
[2]Not including the two patients who died 24 h postoperatively.
Abbreviations: FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; LVEF, left ventricular ejection fraction; NR, not reported; PLTC, platelet concentrate; PRBC, packed red blood cells; RCT, randomised controlled trial.

Citation		
Casati V, Benussi S, Sandrelli L, Grasso MA, Spagnolo S, and D'Angelo A. (2004) Intraoperative Moderate Acute Norvolemic Hemodilution Associated with a Comprehensive Blood-Sparing Protocol in Off-Pump Coronary Surgery. Anesthesia and Analgesia 98:1217-1223.		
Affiliation/Source of funds		
NR		
Study design	Level of evidence	Location/setting
RCT	II	Italy / Hospital
Intervention	Comparator	
ANH + tranexamic acid: intraoperative tranexamic acid as an IV bolus of 1 g 20 min before sternotomy, followed by continuous infusion of 400 mg/h until the end of surgery. The blood shed from the surgical field was collected in a cardiotomy reservoir and, in case of intraoperative bleeding more than 250 mL, reinfused after washing and concentration in a cell salvage circuit. n=50 ANH protocol: The whole-blood volume targeted for removal was 17% ± 2% of the circulating volume, as calculated from a body-surface area nomogram. The blood was drawn after the induction of anesthesia and before systemic heparinization, and was collected into sterile bags containing citrate phosphate dextrose by using a blood mixer and balance system. During blood withdrawl, 4% succinylated gelatine in 0.9% NaCl was infused at a 1:1 ratio. Irrespective of heamatocrit values, reinfusion of the harvested Autologous blood was started after protamine administration and on-demand reinfusion of the shed blood.	Tranexamic acid control: Intraoperative tranexamic acid as an IV bolus of 1 g 20 min before sternotomy, followed by continuous infusion of 400 mg/h until the end of surgery. The blood shed from the surgical field was collected in a cardiotomy reservoir and, in case of intraoperative bleeding more than 250 mL, reinfused after washing and concentration in a cell salvage circuit. n=50	
Population characteristics		
Patients undergoing OPCAB (baseline hematocrit > 34%).		
Length of follow-up	Outcomes measured	
NR	Mortality, perioperative complications (respiratory failure, myocardial infarction, acute renal failure, venous thromboembolism, neurological complications), postoperative bleeding, transfusion frequency of allogeneic blood, units of allogeneic blood transfused, ICU stay, postoperative hospital stay, intubation time.	

INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation randomised, however it is unclear whether allocation to treatment groups was concealed from those responsible for recruiting subjects.	Treatment groups had similar patient demographics and haematochemical levels.	Surgical staff/assessors were not blinded to treatment group. It is unclear whether the participants were blinded to treatment allocation.	Not detected	There was no loss to follow-up. All analyses were performed ITT
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Mortality	0/50 (0%)	1/50 (2%)	-
Morbidity	Respiratory failure: 1/50 (2%) atrial fibrillation: 5/50 (10%) major ventricular arrhythmia: 1/50 (2%) myocardial infarction: 1/50 (2%) creatinine double the baseline: 1/50 (2%) minor neurological complications: 2/50 (4%)	Respiratory failure: 1/50 (2%) atrial fibrillation: 6/50 (12%) major ventricular arrhythmia: 1/50 (2%) myocardial infarction: 1/50 (2%) creatinine double the baseline: 2/50 (4%) minor neurological complications: 1/50 (2%)	P-value Respiratory failure: 1.00 atrial fibrillation: 0.75 major ventricular arrhythmia: 1.00 myocardial infarction: 1.00 creatinine double the baseline: 0.57 minor neurological complications: 0.57
Mean (IQR) total postoperative bleeding (mL)	375 (248, 475)	350 (300, 443)	NS
Mean (IQR) bleeding 0 to 4 h after surgery (mL)	160 (110, 235)	150 (100, 220)	NS
Patients transfused with allogeneic PRBC	2/50 (4%)	10/50 (20%)	P=0.028
Units of allogeneic PRBC transfused	5	24	P<0.001
Total number of patients transfused with allogeneic blood (including PRBC, FFP, and PLTC)	2/50 (4%)	10/50 (20%)	P=0.028
Mean (IQR) ICU stay (d)	1 (1, 1)	1 (1, 1)	P=1
Mean (IQR) postoperative hospital stay (d)	6 (6, 7)	6 (6, 7)	NR
Mean (IQR) intubation time (min)	252 (151, 186)	244 (165, 182)	NR

EXTERNAL VALIDITY
Generalisability
Patients considered similar to guideline target population.
Applicability
RCT performed in Italy; however the results should be applicable to the Australian setting.
Comments

Abbreviations: OPCAB, Off-pump coronary artery bypass

Citation				
Friesen RH, Perryman KM, Weigers KR, Mitchell MB, and Friesen RM. (2006) A trial of fresh autologous whole blood to treat dilutional coagulopathy following cardiopulmonary bypass in infants. Paediatric Anaesthesia 16:429-435.				
Affiliation/Source of funds				
The research was supported by a grant from the General Clinical Research Centers Program, National Center for Research Resources, NIH.				
Study design	Level of evidence		Location/setting	
RCT	II		USA / hospital	
Intervention		Comparator		
Whole blood in the amount of 15 mL/kg was withdrawn from the patient through the central venous catheter. Isovolemia was maintained by infusion of 1 mL of 5% albumin solution for each mL of blood withdrawn. The autologous blood was retransfused postoperatively. n=16		Patients in the control group did not have withdrawal of autologous whole blood or infusion of albumin. n=16		
Population characteristics				
Infants undergoing non-complex open cardiac surgery.				
Length of follow-up		Outcomes measured		
After 2 hours in the ICU.		Primary outcome: Coagulation status (measured by PC, PA, PT, aPTT, and fibrinogen concentration. Secondary outcomes: activation of fibrinolysis (not reported in this form)[1], measured by tissue plasminogen activator, plasminogen activator inhibitor, and d-dimer; haematocrit; 24 h postoperative blood loss, measured as the sanguinous output through the mediastinal drainage tube; and the transfusion of homologous blood components during the intraoperative and 24 h postoperative periods.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was concealed from those responsible for recruiting subjects.	The intervention groups were similar in patient demographics, type of operation, and baseline coagulation tests.	The study was not blinded.	Transfusion protocol was used.	There was no loss to follow-up
Overall quality assessment (descriptive)				
Fair				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Mean (SD) haematocrit, %	T1: 32 (3) T2: 32 (8) T3: 33 (7) T4:35 (8) ΔT2 – T3: +1 (2) ΔT2 – T4: +3 (4)	T1: 32 (4) T2: 34 (6) T3: 34 (6) T4: 34 (5) ΔT2 – T3: +1 (1) ΔT2 – T4: 0 (3)	From T2 to T4, the treatment group had a greater improvement in haematocrit (P=0.009).
Mean (SD) PC, 10^9/L	T1: 353 (92) T2: 126 (49) T3: 161 (55) T4:207 (53) ΔT2 – T3: +36 (22) ΔT2 – T4: +82 (43)	T1: 335 (92) T2: 140 (47) T3: 158 (57) T4: 217 (59) ΔT2 – T3: +18 (17) ΔT2 – T4: +70 (42)	From T2 to T3, the treatment group had greater improvement in PC (P=0.018)
Mean (SD) PA, s	T1: 205 (62) T2: 222 (71) T3: 144 (58) T4: 112 (23) ΔT2 – T3: -78 (53) ΔT2 – T4: -109 (67)	T1: 189 (54) T2: 210 (70) T3: 159 (72) T4: 113 (32) ΔT2 – T3: -49 (77) ΔT2 – T4: -97 (64)	NR
Mean (SD) PT, s	T1: 13.4 (0.9) T2: 20.4 (4.3) T3: 18.1 (3.1) T4: 15.9 (2.1) ΔT2 – T3: -2.3 (1.9) ΔT2 – T4: -4.5 (3.2)	T1: 14.1 (1.1) T2: 19.9 (3.8) T3: 18.9 (3.6) T4:16.8 (2.0) ΔT2 – T3: -0.9 (1.2) ΔT2 – T4: -3.0 (2.7)	From T2 to T3, the treatment group had greater improvement in PT (P=0.015)
Mean (SD) aPTT, s	T1: 35.9 (9.3) T2: 46.7 (14.2) T3: 42.2 (14.1) T4: 37.8 (13.2) ΔT2 – T3: -4.4 (7.7) ΔT2 – T4: -8.9 (11.0)	T1: 36.9 (8.7) T2: 44.1 (12.6) T3: 43.7 (13.1) T4: 41.9 (17.2) ΔT2 – T3: -0.4 (9.6) ΔT2 – T4: -2.3 (16.7)	NR
Mean (SD) fibrinogen concentration, mg/dL	T1: 235 (63) T2: 109 (37) T3: 132 (44) T4: 152 (51) ΔT2 – T3: +14 (9) ΔT2 – T4: +35 (18)	T1: 215 (55) T2: 129 (38) T3: 128 (32) T4: 146 (36) ΔT2 – T3: -1 (16) ΔT2 – T4: +17 (20)	The treatment group had a greater improvement in fibrinogen from T2 to T3 (P=0.003), and T2 to T4 (P=0.019)
Postoperative 24 h blood loss.			Was less in the treatment group when measured as mL per 24 h (P=0.036), but not significantly less when measured as mL/kg.24h (P=0.16).

Transfusion misc.			One subject in the treatment group and five subjects in the control group received postoperative FFP or platelet transfusion (P=0.06).
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The study population was infants, and therefore the study is not generalisable to an adult population.			
Applicability			
The study was conducted in the USA, and the procedures are likely to be comparable to those used in Australia.			
Comments			

[1]Tests of fibrinolysis underwent similar changes in both groups.
Abbreviations: aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; ICU, intensive-care unit; PA, platelet aggregation; PC, platelet count; PT, prothrombin time; T1, baseline; T2, following conclusion of CPB and modified ultrafiltration; T3, 20 min after T2; T4, after 2 hours in the ICU

Citation				
Hohn L, Schweizer A, Licker M, and Morel DR. (2002) Absence of beneficial effect of acute normovolemic hemodilution combined with aprotinin on allogeneic blood transfusion requirements in cardiac surgery. Anesthesiology 96:276-282.				
Affiliation/Source of funds				
The current study was initiated while the authors were in discussion with Biosafe Corporation about the opportunity to test a new blood separator device to evaluate the efficiency of thrombocytapheresis during cardiac surgery.				
Study design	Level of evidence		Location/setting	
RCT	II		Switzerland / university hospital	
Intervention		Comparator		
ANH: ANH was added to the control procedure described. Blood was withdrawn from the mean haematocrit of 43% to 28%. n=39 (although 3 participants were lost to follow up and not included in analysis)		Control: filling of extracorporeal circuit with saline isotonic fluid only, intraoperative blood salvage and reinfusion of shed mediastinal blood, integral reinfusion of blood contained in the extracorporeal circuit at the end of surgery, administration of intravenous aprotinin, and external heating at the end of CPD. n=41		
Population characteristics				
Patients undergoing on-CPB cardiac surgery				
Length of follow-up		Outcomes measured		
Five days after hospital discharge.				
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
The study was randomised however it is not clear whether allocation was concealed from those responsible for recruiting subjects.	The treatment groups had similar preoperative demographics, except that more patients were taking diuretics in the ANH group than in the control group (P=0.001).	The study was not blinded	A transfusion protocol was used.	Three ANH patients (8%) were withdrawn because of postoperative surgical lesion bleeding that needed reoperation for haemostasis (P=0.098 compared with the control group). These patients were not included in further analysis.
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Mean ± SD (range) blood volume collected during ANH, mL	1099 ± 333 (430 to 1900)			
Patients receiving allogeneic blood	12/39 (31%)	12/41 (29%)	P=0.88	

Median (range) number of allogeneic blood units per transfused patient	2 (1 to 5)	2 (1 to 3)	P=0.219
Mean (SD) baseline haematocrit concentration, %	43.3 (3.9)	43.2 (2.4)	P=0.89
Mean (SD) immediate postoperative haematocrit concentration, %	25 (3.5)	25.7 (3.3)	P=0.36
In-hospital mortality	0/39 (0%)	2/41 (5%)	P=0.31
Mean (SD) postoperative length of hospital stay, d	13.1 (3.7)	13.4 (8.3)	P=0.83
Mean (SD) length of ICU stay, d	3.1 (1.3)	3.0 (1.3)	P=0.73
Reoperation for bleeding	3/39 (8%)	0/41 (0%)	P=0.18
Mean (SD) surgical time, min	245 (65)	271 (80)	P=0.11
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients studied were similar to the target population of the guidelines.			
Applicability			
Study was conducted in Switzerland, but is likely to be applicable to the Australian context.			
Comments			

Citation				
Jarnagin WR, Gonen M, Maithel SK, Fong Y, DAngelica MI, Dematteo RP, Grant F, Wuest D, Kundu K, Blumgart LH, and Fischer M. (2008) A prospective randomized trial of acute normovolemic hemodilution compared to standard intraoperative management in patients undergoing major hepatic resection. Annals of Surgery 248:360-368.				
Affiliation/Source of funds				
Authors received financial support from Robert Wittes, MD, Physician-in-Chief, Memorial Hospital				
Study design	Level of evidence	Location/setting		
RCT	II	USA / hospital		
Intervention	Comparator			
ANH: blood was withdrawn to a target Hgb of 8.0 g/dL, with a maximum of 3 L of blood removed. Euvolemia was maintained by replacing half of the removed blood volume with 5% albumin and the other half with crystalloid. n=63	Standard anaesthetic management n=67			
Population characteristics				
Patients undergoing major hepatic resection (3 or more liver segments) for any diagnosis, with or without any other planned procedures.				
Length of follow-up	Outcomes measured			
-	Proportion of patients who required transfusion of allogeneic red blood cell products, impact of ANH on FFP transfusion, intraoperative management, postoperative complications, operating time, and length of stay.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is not clear whether allocation was concealed from those responsible for recruiting subjects.	The groups were well matched for demographic and preoperative variables. The only difference noted was the proportion of patients with comorbid medical conditions, which was higher in the ANH group.	The study was not blinded.	A transfusion protocol was used.	ITT analysis was performed.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Median (range) volume of blood removed during ANH, mL	2250 (800 to 3000)			

Median (range) estimated blood loss, mL	800 (100 to 3200)	700 (100 to 4000)	P=0.42
Median (range) length of surgery, min	255 (135 to 546)	288 (140 to 535)	P=0.35
Patients undergoing any allogeneic transfusion	14/63 (22.2%)	23/67 (34%)	P=0.13
Patients transfused with allogeneic RBC (total)	8/63 (12.7%)	17/67 (25.4%)	P=0.08
Patients transfused with allogeneic RBC (intraoperative)	1/63 (1.6%)	7/67 (10.4%)	P=0.07
Patients transfused with FFP	11/63 (17.5%)	19/67 (28.4%)	P=0.15
Mean (SD) units of allogeneic RBC transfused (for those who received any allogeneic RBC transfusion)	3.5 (1.3)	2.1 (0.5)	P=0.6
Mean (SD) units of any allogeneic transfusion (RBC or FFP; for those who received any RBC or FFP transfusion)	5.6 (1.7)	6.9 (2.7)	P=0.72
Overall morbidity	28/63 (44%)	22/67 (33%)	P=0.17
Grade ≥ 3 morbidity	19/63 (30%)	19/67 (28%)	P=0.82
Median (range) length of hospital stay, d	7 (5 to 50)	7 (4 to 26)	P=0.33
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients studied were similar to the target population of the guidelines.			
Applicability			
The study was conducted in USA, but is likely to be applicable to the Australian context.			
Comments			

Abbreviations: FFP, fresh frozen plasma

Citation				
Juelsgaard P, Moller MB, and Larsen UT. (2002) Preoperative acute normovolaemic hemodilution (ANH) in combination with hypotensive epidural anaesthesia (HEA) during knee arthroplasty surgery. No effect on transfusion rate. A randomized controlled trial [ISRCTN87597684]. BMC Anesthesiology 2.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	Denmark, hospital		
Intervention	Comparator			
ANH: 20% of the total blood volume was drawn before anaesthesia. This volume was simultaneously replaced with an equal volume of Hydroxy Ethyl Starch 6%. Blood re-transfusion was completed within 6 h. n=14	No ANH. n=14			
Population characteristics				
Patients undergoing total knee arthroplasty surgery.				
Length of follow-up	Outcomes measured			
	Amount of allogeneic blood transfused, blood loss			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Patients were randomised, however it is unclear whether the allocation was blinded from those responsible for recruiting subjects.	The participants in the ANH group were older than control: 75.8 (6.4) years vs 70.1 (9.6) years; P=0.008 The control group had a higher mean arterial pressure (mm Hg) compared with ANH: 118 (19) vs 103 (12); P=0.02	The patients were blinded to treatment allocation; however, it is unclear whether the allocation was blinded to the people conducting the trial.	Not detected	There was no loss to follow up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Patients transfused with PRBCs	7/14 (50%)	6/14 (43%)	
Mean volume of PRBCs transfused (mL)	386	343	0.85
Mean (SD) intraoperative blood loss (mL)	131 (78)	111 (56)	0.45

Mean (SD) total blood loss (mL)	1306 (300)	1026 (294)	0.02
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients studied were similar to the target population of the guidelines.			
Applicability			
The study was conducted in Denmark; however it should be applicable to the Australian context.			
Comments			

Citation				
Lim YJ, Kim CS, Bahk JH, Ham BM, and Do SH. (2003) Clinical trial of esmolol-induced controlled hypotension with or without acute normovolemic hemodilution in spinal surgery. Acta Anaesthesiologica Scandinavica 47:74-78.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	South Korea / university hospital		
Intervention	Comparator			
Combined ANH and esmolol-induced controlled hypotension (E-ANH group): for ANH autologous blood was withdrawn from the radial artery aiming for 28% haematocrit. To maintain normovolemia, the first 500 mL of blood drawn was simultaneously replaced with an equal amount of 6% hydroxyethyl starch, and the blood thereafter was replaced with three times that volume of Lactated Ringer's solution. n=15	esmolol-induced controlled hypotention alone (esmolol group): controlled hypotension was performed during the period of bony decompression and instrumental fusion of the spine. Following an initial bolus injection of esmolol 500 μ/kg, esmolol was continuously infused at a rate of 0-300 μg/kg/min to bring the MAP n=15			
Population characteristics				
Patients undergoing spinal surgery				
Length of follow-up	Outcomes measured			
1 week				
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It was not clear whether allocation was concealed from those responsible for recruiting subjects.	There were no significant differences in demographic data between the two groups.	The study was not blinded.	A transfusion protocol was used.	There was no loss to follow-up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group (E-ANH)	Comparator group (esmolol)	Statistical significance
Mean (SE) volume withdrawn during ANH, mL[1]	717 (50)	-	-
Mean (SE) volume of intraoperative bleeding, mL	1600 (160)	1500 (180)	P>0.05
Mean (SE) volume of postoperative bleeding, mL	600 (96)	883 (122)	P>0.05

Mean (SE) concentration of haemoglobin one week postoperative, g%	11.3 (0.3)	11.3 (0.2)	P>0.05
Patients transfused with PRBCs	10/15 (67%)	15/15 (100%)	P=0.04
Mean (SE) units of PRBCs transfused	2.2 (0.6)	4.3 (0.4)	P=0.0052
Morbidity			All patients were evaluated 1 week after the operation, and there were no postoperative complications (thromboembolism, neurologic sequelae or wound infection) in either group.
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients studied were similar to the target population of the guidelines.			
Applicability			
The study was conducted in South Korea; however it should be applicable to the Australian context.			
Comments			

[1]All autologous blood was returned to the patients postoperatively.
Abbreviations: MAP, mean arterial pressure

Citation				
Matot I, Scheinin O, Jurim O, and Eid A. (2002) Effectiveness of acute normovolemic hemodilution to minimize allogeneic blood transfusion in major liver resections. Anesthesiology 97:794-800.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	Israel, medical centre		
Intervention	Comparator			
ANH: Preoperatively, blood was transfused from the patients into standard citrate-phosphate-dextrose blood storage bags, and was simultaneously replaced by colloid solutions. The volume of blood collected was 2,020 ± 412 mL. n=39	No ANH n=39			
Population characteristics				
Patients undergoing liver resection.				
Length of follow-up	Outcomes measured			
NR				
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was randomised; however, it is unclear whether allocation to treatment groups was concealed from those responsible for recruiting subjects.	The treatment arms were similar in baseline characteristics.	Although the surgical staff were not blinded, the investigator who verified the electrocardiogram for possible ischemic episodes was blinded to group assignment. It is unclear the participants were blinded to treatment assignment.	Not detected.	There was no loss to follow up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Mortality	0/39 (0%)	0/39 (0%)	Not estimable
Morbidity (adverse cardiac, renal, or neurological outcomes	0/39 (0%)	0/39 (0%)	Not estimable
Patients receiving PRBCs	4/39 (10%)	14/39 (36%)	P=0.014
Haematocrit (%) (before vs after)	40.8 ± 2.7 vs 23.5 ± 1.2 (P<0.05)	41.6 ± 3.2 vs 40.9 ± 2.8 (P>0.05)	

Mean surgical blood loss (mL)	1442 ± 1827	1528 ± 1822	
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
This trial was conducted on a specific patient population (people undergoing liver resection), however it is likely to be generalisable to patients undergoing other elective surgical procedures with moderate blood loss.			
Applicability			
The study was performed in Israel, which may limit its applicability in the Australian context.			
Comments			

Citation				
Obasi C, Arendt J, and Antoszewski Z. (2006) An assessment of the efficacy of preoperative controlled haemodilution in the perioperative management of patients including the elderly. Chirurgia Polska 8:111-124.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	Poland / hospital		
Intervention	Comparator			
ANH: n=31	Control: n=31			
Population characteristics				
Patients undergoing surgical procedures: endoprosthesis of hip joint (13% ANH vs 10% control); anastomis of the femur for fracture (23% ANH vs 29% control); leg amputation (16% ANH vs 19% control); plastic perineal surgery (13% ANH vs 13% control); gastrointestinal anastomosis (6% in both groups).				
Length of follow-up	Outcomes measured			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is unclear whether allocation was concealed from those responsible for recruiting subjects. Randomisation method was not disclosed.	The percentage of patient > 70 years was 52% in the ANH group and 39% in the control group. Other baseline characteristics were similar between the groups.	The study was not blinded.	There was no transfusion protocol.	There was no loss to follow up.
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Mean (SD) preoperative concentration of haemoglobin, mmol/L	8.37 (0.43)	8.37 (0.63)	NS	
Mean (SD) concentration of haemoglobin immediately postoperative, mmol/L	6.45 (0.52)	6.46 (0.56)	NS	
Mean (SD) concentration of haemoglobin 6 hours postoperative, mmol/L	7.20 (0.53)	6.48 (0.56)	P<0.005	

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
Patients studied were similar to the target population of the guidelines.	
Applicability	
The study was conducted in Poland; which may limit its applicability to the Australian context.	
Comments	

Citation				
Sanders G, Mellor N, Rickards K, Rushton A, Christie I, Nicholl J, Copplestone A, and Hosie K. (2004) Prospective randomized controlled trial of acute normovolaemic haemodilution in major gastrointestinal surgery. British Journal of Anaesthesia 93:775-781.				
Affiliation/Source of funds				
NR				
Study design	Level of evidence		Location/setting	
RCT	II		UK, hospital	
Intervention		Comparator		
ANH: Maximum 3 units of blood withdrawn and transfused into blood bags containing citrate-phosphate-dextrose (anticoagulant). Warmed cell-free fluid was administered during blood withdrawal to maintain normovolaemia. At the end of the operation, all the autologous blood was re-transfused. n=78		No ANH n=82		
Population characteristics				
Patients undergoing major gastrointestinal surgery (colorectal, gastric, or pancreatic). These operations were considered high risk (>40%) for allogeneic transfusion.				
Length of follow-up		Outcomes measured		
NR (at least 3 days)		Proportion of patients transfused with allogeneic red blood cells, number of units transfused in the first 3 days after surgery, time taken to venesect, perioperative complications, hospital length of stay.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Patients were randomised to treatment arm, however it is unclear whether allocation was concealed from the people responsible for recruiting participants.	Treatment groups were similar in baseline characteristics. There was a statistically significant difference between the groups, in both preoperative and postoperative temperature (P<0.01); however, the difference in median temperatures was 0.1 and 0.3°C, respectively.	The patients were blinded; however, the surgical team were not blinded.	None detected. Transfusion protocol was not overruled for any of the patients.	There was no loss to follow-up
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	

Mortality	2/78 (3%)	1/82 (1%)	NR
Morbidity	Pyrexia: 0/78 (0%) UTI: 8/78 (10%) RTI: 2/78 (3%) Wound infection: 3/78 (4%) Deep infection: 1/78 (1%) Septicaemia: 1/78 (1%) DVT: 2/78 (3%) PE: 0/78 (0%) Anastomotic leak: 0/78 (0%)	Pyrexia: 3/82 (4%) UTI: 7/82 (9%) RTI: 1/82 (1%) Wound infection: 6/82 (7%) Deep infection: 0/78 (0%) Septicaemia: 1/82 (1%) DVT: 2/82 (2%) PE: 2/82 (2%) Anastomotic leak: 3/82 (4%)	Pyrexia: P=0.21 UTI: P=0.71 RTI: P=0.54 Wound infection: P=0.35 Deep infection: P=0.48 Septicaemia: P=0.97 DVT: P=0.96 PE: P=0.31 Anastomotic leak: P=0.21
Patients receiving allogeneic blood	22/78 (28%)	25/82 (30%)	NS
Units of allogeneic blood transfused.	90	93	NS
Median (range) blood loss (mL)	750-1000 (100-4500)	750-1000 (100-4368)	
Median (range) length of hospital stay, d	8 (5 to 110)	10 (5 to 92)	NS
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The study population was people undergoing major gastrointestinal surgery; however, the study is likely to be somewhat generalisable for surgical procedures with a high likelihood for transfusion.			
Applicability			
Study performed in Canada which has many similarities with the Aus/NZ healthcare systems.			
Comments			

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; RTI, respiratory tract infection; UTI, urinary tract infection.

Citation				
Saricaoglu F, Akinci SB, and Aypar U. (2005) The effect of acute normovolemic hemodilution and acute hypervolemic hemodilution on coagulation and allogeneic transfusion. Saudi Medical Journal 26:792-798.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	Turkey / University hospital		
Intervention	Comparators			
ANH: Autologous blood 15 mL/kg was withdrawn and replaced by ~15 mL/kg 6% HES n=10	HHD: 15 mL/kg HES administered without removal of any autologous blood n=10 Control: no haemodilution n=10			
Population characteristics				
Patients undergoing hip arthroplasty.				
Length of follow-up	Outcomes measured			
24 h postoperative				
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was concealed from those responsible for recruiting subjects.	The 3 groups were similar regarding age, gender, height, weight, duration of operation, intraoperative blood loss, postoperative drainage, and the amount of intraoperative crystalloid infused (p>0.05)	The study was not blinded.	A transfusion protocol was used.	There was no loss to follow-up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Median (95% CI) volume of blood withdrawn during ANH, mL	1065 (975, 1170)		
Median (95% CI) intraoperative blood loss, mL	740 (600, 830)	HHD: 650 (500, 855) Control: 695 (510, 855)	P=0.275
Median (95% CI) duration of operation, min	105 (95, 125)	HHD: 102.5 (95, 125) Control: 105 (95, 125)	P=0.795

Patients transfused with allogeneic RBCs	2/10 (20%)	HDD: 4/10 (40%) Control: 10/10 (100%)	
Total units of allogeneic RBCs transfused	3 (one patient required 1 unit and the other required 2)	HDD: 5 (three patients required one unit and one patient required 2 units) Control: 13 (7 patients required one unit and 3 patients required 2 units)	P(ANH+HDD vs control)<0.05
Median (95% CI) preoperative haematocrit concentration, %	39.2 (34.6, 46.0)	HHD: 41.1 (37, 45.3) Control: 43.2 (35.8, 45.8)	P=0.5
Median (95% CI) postoperative haematocrit concentration, %	32.7 (26.5, 38.6)	HHD: 29.1 (26.5, 38.6) Control: 32.3 (26.5, 38.6)	P=0.398
Median (95% CI) 24 h postoperative haematocrit concentration, %	32.7 (30.1, 40.1)	HHD: 34.9 (30.2, 36.7) Control: 32.9 (30, 36.5)	P=0.89
Mean (95% CI) preoperative platelet count, 1000/mm^3	280 (132, 367)	HDD: 286 (240, 387) Control: 285 (240, 387)	P=0.98
Mean (95% CI) postoperative platelet count, 1000/mm^3	258 (123, 354)	HDD: 204 (167, 300) Control: 241 (175, 310)	P=0.96
Mean (95% CI) 24 h postoperative platelet count, 1000/mm^3	283 (138, 356)	HDD: 195 (163, 300) Control: 283 (190, 356)	P=0.010
Mean (95% CI) preoperative INR	1.1 (0.92, 1.3)	HDD: 1.15 (0.95, 1.4) Control: 1.15 (0.92, 1.14)	P=0.6
Mean (95% CI) postoperative INR	1.2 (1.1, 2.3)	HDD: 1.4 (1.2, 1.5) Control: 1.35 (1.2, 1.5)	P=0.052
Mean (95% CI) 24 h postoperative INR	1.2 (1.1, 1.87)	HDD: 1.2 (1.1, 1.3) Control: 1.2 (1.1, 1.3)	P=0.68
Mean (95% CI) preoperative aPTT, seconds	27.6 (26.4, 35.9)	HDD: 28.5 (26.8, 32.1) Control: 27.6 (26.4, 32.1)	P=0.4
Mean (95% CI) postoperative aPTT, seconds	26.75 (23.8, 32.3)	HDD: 33.8 (30.1, 35.6) Control: 27.5 (24.7, 34.2)	P=0.01 P(ANH v HDD)<0.008
Mean (95% CI) 24 h postoperative aPTT, seconds	26.5 (24.7, 30.1)	HDD: 30.1 (24.7, 34.2) Control: 24.2 (24.2, 34.7)	P=0.182
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients studied were similar to the target population of the guidelines.			
Applicability			
The study was conducted in Turkey; which may limit its applicability to the Australian context.			
Comments			

Abbreviations: HES, hydroxyethyl starch; HHD, hypervolemic haemodilution; INR, international normalised ratio; aPTT, activated partial thromboplastin time

<table>
<tr><td colspan="5">Citation</td></tr>
<tr><td colspan="5">Wolowczyk L, Nevin M, Smith FCT, Baird RN, and Lamont PM. (2003) Haemodilutional effect of standard fluid management limits the effectiveness of acute normovolaemic haemodilution in AAA surgery - Results of a pilot trial. European Journal of Vascular and Endovascular 26:405-411.</td></tr>
<tr><td colspan="5">Affiliation/Source of funds</td></tr>
<tr><td colspan="5">None declared.</td></tr>
<tr><td colspan="2">Study design</td><td colspan="2">Level of evidence</td><td>Location/setting</td></tr>
<tr><td colspan="2">RCT</td><td colspan="2">II</td><td>UK / hospital</td></tr>
<tr><td colspan="3">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="3">ANH and cell salvage: 15 g/kg of blood was withdrawn and replaced with a similar volume of 6% HAES
n=18 (although two patients were not included in the</td><td colspan="2">Standard care (including cell salvage)
n=18</td></tr>
<tr><td colspan="5">Population characteristics</td></tr>
<tr><td colspan="5">Patients undergoing abdominal aortic aneurysm repair.</td></tr>
<tr><td colspan="3">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="3">Seven days postoperative</td><td colspan="2"></td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation</td><td>Results</td><td>Blinding analysis</td><td>Treatment/measurement bias</td><td>Follow-up (ITT)</td></tr>
<tr><td>It is unclear whether allocation was concealed from those responsible for recruiting subjects.</td><td>Both groups were well matched. The incidence of ischemic heart disease in the form of previous myocardial infarction and/or angina was similer: 5/16 ANH and 7/18 control patients. One patient randomised to the ANH group had a successful coronary artery bypass graft prior to AAA repair. All AAAs were infra-renal, but supra-renal aortic clamping was necessary in 2 ANH and 3 control patients.</td><td>The study was not blinded.</td><td>A transfusion protocol was used.</td><td>The study was not performed ITT. Two patients randomised into the ANH group exhibited signs of poor cardiac reserve soon after induction of general anaesthesia, which precluded the ANH. Those two patients were excluded from further analysis.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive)</td></tr>
<tr><td colspan="5">Fair</td></tr>
</table>

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Median (range) amount of blood withdrawn during ANH, g	890 (670, 1620)	-	-
Median (IQR) intraoperative blood loss, mL	1780 (930, 5000)	1700 (750, 2600)	P=0.55
Patients with blood loss below 1000 mL	4/16 (25%)	5/18 (28%)	P=1.0
Median (IQR) volume of RBCs concentrate recovered by intraoperative cell salvage and retransfused	590 (200, 1410)	540 (210, 740)	P=0.60
Patients transfused with banked autologous blood intraoperatively	7/16 (44%)	7/18 (39%)	P=1
Patients transfused with banked autologous blood postoperatively	5/16 (31%)	10/18 (56%)	P=0.73
Total patients transfused with banked autologous blood(intraoperatively and postoperatively)	10/16 (63%)	13/18 (72%)	P=0.99
Median (IQR) units of banked autologous blood transfused intraoperatively	0 (0 to 4)	0 (0 to 2)	P=0.51
Median (IQR) units of banked autologous blood transfused postoperatively	0 (0 to 2)	1 (0 to 2)	P=0.33
Median (IQR) units of banked autologous blood transfused (intraoperatively and postoperatively)	2 (0 to 5)	2.5 (0 to 5)	P=0.68
Median (range) Haemoglobin concentration, g/dL	Preoperative: 14.2 (12.1 to 16.5) Post-ANH: 9.4 (7.0 to 12.1) At aortic clamping: 9.2 (6.8 to 10.6) At clamp release: 7.7 (6.6 to 9.3) Post-op 1-2 h: 10.8 (8.8 to 13.3) Post-op day 1: 10.4 (8.3 to 12.4) Post-op day 2: 10.6 (8.2 to 13.3) Post-op day 7: 11.5 (10.2 to 12.4)	Preoperative: 13.8 (12.1 to 15.6) Post-ANH: NA At aortic clamping: 11.3 (7.2 to 14.5) At clamp release: 9.1 (5.1 to 11.9) Post-op 1-2 h:10.3 (8.1 to 12.7) Post-op day 1: 10.4 (8.2 to 12.8) Post-op day 2: 9.7 (8.5 to 13.7) Post-op day 7: 10.7 (9.1 to 11.9)	P-value Preoperative: 0.57 Post-ANH: NA At aortic clamping: 0.001 At clamp release: 0.004 Post-op 1-2 h: 0.68 Post-op day 1: 0.68 Post-op day 2: 0.60 Post-op day 7: 0.021

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
The study population was people undergoing abdominal aortic repair; however, the study is likely to be somewhat generalisable for surgical procedures with moderate blood loss.	
Applicability	
The study is likely to be applicable to the Australian context.	
Comments	

Abbreviations: HAES, hydroxyethyl starch

Intervention 2 – Intraoperative cell salvage

Level I evidence

Citation				
Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine 14:123-144.				
Affiliation/Source of funds				
Research supported by a grant obtained from the National Health and Medical Research Council of Australia and a special purpose grant from the Hunter Area Pathology Service, Australia				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs and observational studies with meta-analysis Search conducted July 2002	I	NA		
Intervention	Comparator			
Autologous transfusion techniques: preoperative Autologous blood deposit (PAD), ANH, and cell salvage (CS). NOTE: This form only contains RCT info relevant for intraoperative cell salvage. Sample size (perioperative cell salvage) N=1073	Comparator: No Autologous transfusion technique (active versus active comparisons were excluded) Sample size (control for perioperative cell salvage) N=1052			
Population characteristics				
Patients older than 18 years undergoing any type of surgery. Fourteen trials involved cardiac surgery, 12 involved orthopaedic surgery, and four involved vascular surgery. The mean age of participants was 64 years. Almost twice as many males as females were studies (1.8:1).				
Length of follow-up	Outcomes measured			
NA	Mortality, re-operation, infection, wound complication, thrombosis, non-fatal MI, rate of allogeneic red blood cell transfusion, and volume of allogeneic blood transfused.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Both the allocation concealment and the method of randomisation were judged by the authors to be inadequate in every case.	SR did not discuss similarity between preoperative data and baseline characteristics for the intervention groups.	The majority of the trials were unblended (96%).	For quality assessment, the agreement between the two SR raters were moderate to good (kappa=0.65 to 1.0)	NR
Overall quality assessment (descriptive)				
Fair				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS) 26 trials (N=1939; 973 cell salvage, 966 control)			RR (95% CI): 0.58 (0.47, 0.73) P*het*<0.00001
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS): transfusion protocol used 23 trials (N=NR)			RR (95% CI): 0.62 (0.50, 0.78) P*het*=NR
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS): no transfusion protocol used/reported 3 trials (N=NR)			RR (95% CI): 0.14 (0.00, 4.48) P*het*=NR
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS): cell washing used 13 trials (N=NR)			RR (95% CI): 0.52 (0.38, 0.71) P*het*=NR
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS): cell washing not used/reported 12 trials (N=NR)			RR (95% CI): 0.74 (0.58, 0.94) P*het*=NR
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS): cardiac surgery 12 trials (N=NR)			RR (95% CI): 0.82 (0.70, 0.95) P*het*=NR
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS): orthopaedic surgery 11 trials (N=NR)			RR (95% CI): 0.35 (0.24, 0.52) P*het*=NR
Number of subjects exposed to allogeneic RBC transfusion (perioperative CS): miscellaneous surgery 3 trials (N=NR)			RR (95% CI): 0.55 (0.13, 2.36) P*het*=NR
Number of subjects exposed to allogeneic RBC transfusion (intraoperative CS) 5 trials (N=NR)			RR (95% CI): 0.61 (0.39, 0.95) P*het*=NR

Mean (95% CI) units of allogeneic blood transfused (intra- and postoperative) 17 trials (N=NR)			RR (95% CI): 0.91 (0.51, 1.31) P*het*<0.00001
Length of hospital stay (intra- and postoperative), days 5 trials (N=NR)			WMD (95% CI): -1.28 (-2.65, 0.08) P*het*=NR
Mortality (intra- and postoperative) 11 trials (N=NR)			RR (95% CI): 1.53 (0.65, 3.61) P*het*=0.66
Infection (intra- and postoperative) 9 trials (N=NR)			RR (95% CI): 0.75 (0.41, 1.37) P*het*=0.37
Wound complications (intra- and postoperative) 7 trials (N=NR)			RR (95% CI): 0.88 (0.42, 1.81) P*het*=NR
Thrombosis (intra- and postoperative) 6 trials (N=NR)			RR (95% CI): 1.46 (0.56, 3.83) P*het*=NR
Non-fatal MI (intra- and postoperative) 5 trials (N=NR)			RR (95% CI): 0.58 (0.28, 1.19) P*het*=NR
Re-operation (intra- and postoperative) 8 trials (N=NR)			RR (95%CI): 1.08 (0.47, 2.48) P*het*=NR
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population			
Applicability			
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).			
Comments			
According to the authors, 5 trials assessed the use of intraoperative CS. The authors do not identify these papers nor do they state the number of participants in the trials.			

Citation				
Carless PA, Henry DA, Moxey AJ, O'connell DL, Brown T, and Fergusson DA. (2006) Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane database of reviews; Issue 4.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR Jan 2004	I	NA		
Intervention	Comparator			
Cell salvage. Studies with a combination of active comparisons were included if both the intervention and control groups were equally exposed to the active treatment (ie, active plus cell salvage versus active comparisons). n (perioperative cell salvage): 1952 n (intraoperative cell salvage): 282 n (postoperative cell salvage): 1448 n (intra- + postoperative cell salvage): 142 The authors found 51 studies.	Any n (perioperative cell salvage): 1905 n (intraoperative cell salvage): 282 n (postoperative cell salvage): 1429 n (intra- + postoperative cell salvage): 152			
Population characteristics				
Adults (over 18 years) undergoing elective, non-urgent surgery. Surgery types found in the search include cardiac (23 studies), orthopaedic (23 studies), and vascular (5 studies) surgery. 33 of the trials studied cell salvage during the postoperative period, 10 studied intraoperative cell salvage, and seven studied both intraoperative and postoperative cell salvage. One trial failed to describe the timing of cell salvage. Twenty trials studied cell salvage systems that reinfused washed salvaged blood, and 29 trials studied cell salvage systems that reinfused unwashed filtered salvaged blood. One trial studied both washed and unwashed cell salvage (4-arm trial) and provided two comparisons of cell salvage. 38 trials reported the use of transfusion protocols.				
Length of follow-up	Outcomes measured			
NA	Number of patients transfused with allogeneic and/or autologous blood, amounts of allogeneic and/or autologous blood transfused, re-operation for bleeding, postoperative complications, mortality, and length of hospital stay.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
According to the authors, the description of the method to conceal allocation of either inadequate or unclear for all of the studies.	-	Based on the Schulz criteria, blinding was reported in only one of the trials.	Nine of the 51 studies did not report a transfusion protocol.	-

Overall quality assessment (descriptive)			
Good			
RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Rate of allogeneic transfusion (intraoperative cell salvage; aggregated analysis[1]) 7 trials (N=564; 282 cell salvage, 282 control)			RR (95% CI): 0.53 (0.35, 0.80) P=0.0027 (P*het*=0.00015)
Rate of allogeneic transfusion (intraoperative cell salvage; active vs control) 5 trials (N=382; 191 cell salvage, 191 control)	76/191 (40%)	113/191 (59%)	RR (95% CI): 0.61 (0.39, 0.95) P=0.029 (P*het*=0.01)
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The SR is generalisable for elective, non urgent surgery.			
Applicability			
The studies were mostly from countries with similar health-care systems to Australia			
Comments			
The systematic review includes trials assessing the intraoperative, postoperative, and both intra- and postoperative. There is more data but most of it combines intra- and postoperative data.			

[1] Includes both studies where an active treatment is compared with a control intervention and those studies where both the intervention and control arms also received an additional active intervention (c.f. active versus control, where the controls are untreated).
Abbreviations: RR, relative risk; ARR, absolute risk reduction; RRR, relative risk reduction; RD, risk reduction

Citation		
Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, and McCollum C. (2006) Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: A systematic review and economic model. Health Technology Assessment 10:1-114.		
Affiliation/Source of funds		
One author received sponsorship from haemonetics and AstraTech to attend the International Society of Blood Transfusion (ISBT) VIIIth European Congress. The author has also given invited lectures for AstraTech Ltd and Unomedical with honoraria and expenses paid.		
Study design	Level of evidence	Location/setting
SR with economic analysis (SR search is an update of Carless 2003: a Cochrane review that had been updated in 2006. The study includes a meta-analysis combining the results of Carless 2003 and the search update. Search conducted Jan 2004.	I	NA
Intervention	Comparator	
Transfusion strategies to minimise perioperative allogeneic blood transfusion: cell salvage, PAD, PAD plus EPO, EPO, ANH, cell salvage plus ANH, AFs, FSs, restrictive transfusion thresholds or protocols. NB: This form only includes information relevant for perioperative cell salvage. Specific characteristics of the 1 included RCT (Zhao 2003) Non-washed shed mediastinal blood retransfused postoperatively after CABG; mean 280 mL autologous blood retransfused/	No cell salvage or allogeneic blood.	
Population characteristics		
For inclusion, the SRs had to only include adults undergoing elective, non-urgent surgery. Specific characteristics of participants in the 1 included RCT (Zhao 2003) Patients undergoing CABG surgery Mean (SD) age (study vs control): 59.2 (8.2) vs 59.5 (8) Sex (M/F): 27/3 vs 26/4		
Length of follow-up	Outcomes measured	
NA	Proportion/number of patients transfused with allogeneic and/or autologous blood; the volume of allogeneic and/or autologous blood transfused; reoperation for bleeding; adverse transfusion reactions; preoperative morbidity and Hb levels; postoperative complications; length of hospital stay; mortality.	

INTERNAL VALIDITY[1]				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Method of randomisation not described and allocation concealment unclear.	Zhao 2003 had adequate baseline comparability.	Did not have participant blinding and it is unclear whether study had allocation concealment.	The study had a well defined transfusion protocol.	Unclear intention to treat (however there was no loss to follow-up).
Overall quality assessment (descriptive)				
Good				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Number of patients transfused with allogeneic blood (intraoperative cell salvage; active versus control[2]) 5 trials (N=382; 191 cell salvage, 191 control)	74/191 (41%)	113/191 (59%)	RR (95% CI): 0.61 (0.39, 0.95) P*het*=0.01	
Clinical importance		Clinical relevance		
EXTERNAL VALIDITY				
Generalisability				
The review includes all surgery types and performs subgroup analyses by surgery type. Therefore the results are likely to be generalisable for other elective, non-emergency operations.				
Applicability				
Low applicability to the question - With the exception of transfusion frequency, all of the outcomes assessed combined data from intra- and postoperative cell salvage.				
Comments				
The updated lit search included 2 RCTs (1 as abstract only): Naumenko 2003 and Zhao 2003. Zhao 2003 investigated intraoperative cell salvage (described in this form), and Naumenko investigated postoperative cell salvage (described in I4).				

[1]Refers only to the one intraoperative cell salvage RCT included in the systematic update (Zhao 2003)
[2]Does not include studies where both the intervention and control arms received an additional active intervention.
[3]Combines data from 5 trials using intraoperative cell salvage, 18 trials of postoperative cell salvage and 5 trials assessing combined intra- + postoperative cell salvage.
[4]Includes both studies where an active treatment is compared with a control intervention and those studies where both the intervention and control arms also received an additional active intervention. Includes cell salvage in both the intra- and postoperative periods.
Abbreviations: CABG, Coronary Artery Bypass Graft; MI, myocardial infarction

Citation				
Huet C, Salmi R, Fergusson D, Koopman-Van Gemert AWMM, Rubens F, and Laupacis A. (1999) A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. Anesthesia and Analgesia 89:861-869.				
Affiliation/Source of funds				
Coordinating Centre has been funded by Janssen Ortho Inc, Canada. One of the authors is the recipient of the First Fellowship from the International Society of Technology Assessment in Health Care, funded by the PPP Medical Trust.				
Study design	Level of evidence	Location/setting		
SR of RCTS with Meta-analysis Search conducted 1997	I	NA		
Intervention	Comparator			
Intraoperative cell salvage	Control			
Population characteristics				
Patients who underwent cardiac or orthopaedic surgery (two articles dealing with vascular surgery were not considered). The one study for intraoperative cell salvage included was in patients undergoing hip surgery.				
Length of follow-up	Outcomes measured			
NA	Proportion of patients receiving at least one unit of allogeneic packed red blood cells			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Three of the included trials were pseudo-randomised.		Unclear: "all of the 28 trials included in this study scored between zero and three on the Jadad scale. Because it is difficult to "blind" the operative team to the presence or absence of cell salvage, the Jadad score would rarely be expected to be greater than 3"	The SR did not report on whether or not a transfusion protocol was used in the RCTs	NR
Overall quality assessment (descriptive)				
Good				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Patients transfused with allogeneic blood 1 trial (N=40; 20 cell salvage, 20 control)	6/20 (30%)	18/20 (90%)	RR (95% CI): 0.33 (0.17, 0.66) P<0.05 (P*het*=NA)	

Mean units of allogeneic blood transfused 1 trial (N=40; 20 cell salvage, 20 control)	0.7	2.7	NR
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The review includes all surgery types and performs subgroup analyses by surgery type. Therefore the results are likely to be generalisable for other elective, non-emergency operations.			
Applicability			
Low applicability to the question - all of the outcomes assessed combined data from intra- and postoperative cell salvage.			
Comments			
1 trial for intraoperative cell salvage included			

[1]Includes both studies where an active treatment is compared with a control intervention and those studies where both the intervention and control arms also received an additional active intervention (c.f. active versus control, where the controls are untreated).

Citation				
Takagi H, Sekino S, Kato T, Matsuno Y, and Umemoto T. (2007) Intraoperative autotransfusion in abdominal aortic aneurysm surgery: meta-analysis of randomized controlled trials (Structured abstract). Archives of Surgery 142:1098-1101.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR November 2005	I	NA		
Intervention	Comparator			
Intraoperative autotransfusion	Control			
Population characteristics				
Patients undergoing elective infrarenal abdominal aortic aneurysm surgery.				
Length of follow-up	Outcomes measured			
NR	Incidence of allogeneic blood transfusion			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is not clear whether any of the trials concealed allocation from those responsible for recruiting subjects.	The studies had similar baseline characteristics between active and control treatments.	The surgery teams were not blinded in any of the studies.		
Overall quality assessment (descriptive)				
Good				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Number of patients who received allogeneic transfusion 4 trials (N=292)	67/147 (45.6)	109/145 (75.1)	RR (95% CI): 0.63 (0.41, 0.95) P<0.05 (P*het*=0.02)	
Clinical importance	Clinical relevance			
EXTERNAL VALIDITY				
Generalisability				
The study populations are similar to the guideline population.				

Applicability
The results are applicable to the Australian context.
Comments

Level II evidence

Citation				
Bowley DM, Barker P, and Boffard KD. (2006) Intraoperative blood salvage in penetrating abdominal trauma: A randomised, controlled trial. World Journal of Surgery 30:1074-1080.				
Affiliation/Source of funds				
NR				
Study design	Level of evidence		Location/setting	
RCT	II		Johannesburg (Republic of South Africa), hospital	
Intervention		Comparator		
Intraoperative blood salvage with transfusion of both allogeneic and washed autologous blood. N=21		Allogeneic blood transfusion at the discretion of the attending medical staff. N=23		
Population characteristics				
Patients with penetrating torso injury requiring a laparotomy and who had exhibited hypotension either pre-hospital or on arrival and in whom there was considered to be significant blood loss.				
Length of follow-up		Outcomes measured		
24 hours post-injury		Volume of allogeneic blood transfused, mortality		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Patients were randomised and allocation was concealed	Patients had similar baseline characteristics in terms of pre-hospital time (when known), ER to OR time, Revised Trauma Score, Injury Severity Score, Penetrating Injury Severity Score, and number of organs injured.	The intervention was not blinded.	Transfusion protocol NR.	It is unclear whether the analyses were conducted ITT.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Mean volume (units) of allogeneic blood transfused	6.47 (5.14)	11.17 (6.06)	P=0.008	
Mortality	14/21 (67%)	15/23 (65%)	P=NS	
Mean length of hospital stay (days)	15.7 (9.17)	14.6 (6.8)	P=0.79	

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
The study assessed the use of cell salvage in traumatic surgery. Therefore, the study is not generalisable for elective, non-emergency surgery.	
Applicability	
The study was conducted in Johannesburg, which may limit the applicability of the study.	
Comments	
The mean volume of salvaged blood retransfused in the cell salvage group: 1493 mL ± 617.43 mL.	

Citation				
Damgaard S and Steinbruchel DA. (2006) Autotransfusion with cell saver for off-pump coronary artery bypass surgery: A randomized trial. Scandinavian Cardiovascular Journal 40:194-198.				
Affiliation/Source of funds				
One of the authors was funded by a research grant from H:S Copenhagen Hospital Corporation				
Study design	Level of evidence		Location/setting	
RCT	I		Denmark, hospital	
Intervention		Comparator		
The continuously heparinised suction and reservoir belonging to the cell saver were used for all patients in both groups. The suctioned blood from patients in the cell saver group was processed and autotransfused before the patient was transferred to the ICU. N=30		Control group had their suctioned blood discharged. N=30		
Population characteristics				
Patients admitted for elective or sub-acute coronary bypass surgery without heart-lung machine.				
Length of follow-up		Outcomes measured		
		Proportion of patients receiving transfusion with allogeneic blood components, average number of units transfused per patient during the admission, intraoperative and postoperative bleeding, changes in haemoglobin and haematocrit, and registration of complications and costs.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Participants were	The intervention groups had similar baseline characteristics. Cell saver group patients received median 1.26 mL of autologous cell saver blood.	Both treatment and control groups underwent blood salvage. Randomisation to blood retransfusion or discharge did not occur until after the operation. Therefore the surgical and anaesthetic team were blinded during the operation, but not after. However, the ICU and ward personnel were not informed about which procedure had been performed.	A transfusion protocol was used.	Intraoperatively, one patient in the control group was excluded (before randomisation). Due to logistic or technical problems the cell saver was not used for five patients in the cell saver group. According to intention to treat principles, they were kept in the study analysis.
Overall quality assessment (descriptive)				
Good				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Patients receiving allogeneic blood components	17/30 (57%)	21/29 (72%)	P=0.28
Median (IQR) volume (units) of allogeneic blood components transfused per patient	1 (0 to 2)	2 (0 to 7)	P=0.06
Median (IQR) units of allogeneic RBCs transfused per patient	1 (0 to 2)	2 (0 to 5)	P=0.07
Median (IQR) units of FFP transfused (ICU)	0 (0 to 0) (range: 0 to 4)	0 (0,0) (range: 0 to 22)	P=0.40
Median (IQR) units of FFP transfused (ward)	0	0 (0, 0) (range: 0 to 1)	P=0.31
Median (IQR) units of pooled platelets transfused	0 (0 to 0) (range:0 to 1)	0 (0 to 0) (range: 0 to 1)	P=NR
Median (IQR) haemoglobin, intensive care (lowest), mmole/L	5.9 (5.3 to 6.6)	5.8 (5.2 to 6.7)	P=0.97
Median (IQR) haematocrit, intensive care (lowest), %	29 (27 to 33)	29 (25 to 33)	P=0.69
Median (IQR) haemoglobin, ward (lowest), mmole/L	6.4 (5.9 to 6.8)	6.6 (5.8 to 7.1)	P=0.58
Median (IQR) haemoglobin, at discharge, %	7.1 (6.5 to 7.4)	7.2 (6.5 to 8.1)	P=0.25
Median (IQR) duration of operation, min	165 (135 to 186)	150 (135 to 188)	P=0.39
Median (IQR) net blood less, mL	300 (193 to 403)	610 (450 to 928)	P<0.001
Mortality	0/30 (0%)	2/30 (7%)	P=0.24

Morbidity	Stroke: 0/30 (0%) MI: 0/30 (0%) Reoperation for bleeding: 1/30 (3%) Pneumonia: 2/30 (7%) GI bleeding: 0/30 (0%) Deep sterna wound infection: 0/30 (0%) Leg wound infection: 0/30 (0%) Dialysis: 1/30 (3%) Ventilator > 24 hours: 0/30 (0%) Low cardiac output syndrome: 0/30 (0%) Atrial arrhythmia: 14/30 (47%) Ventricular arrhythmia: 0/30 (0%) Inotropic infusion: 6/30 (20%)	Stroke: 1/30 (3%) MI: 1/30 (3%) Reoperation for bleeding: 3/30 (10%) Pneumonia: 3/30 (10%) GI bleeding: 3/30 (10%) Deep sterna wound infection: 1/30 (3%) Leg wound infection: 1/30 (3%) Dialysis: 2/30 (7%) Ventilator > 24 hours: 3/30 (10%) Low cardiac output syndrome: 6/30 (20%) Atrial arrhythmia: 20/30 (67%) Ventricular arrhythmia: 3/30 (10%) Inotropic infusion: 9/30 (30%)	P-value Stroke: NS MI: NS Reoperation for bleeding: 0.35 Pneumonia: NS GI bleeding: 0.11 Deep sterna wound infection: NS Leg wound infection: NS Dialysis: NS Ventilator > 24 hours: 0.11 Low cardiac output syndrome: 0.01 Atrial arrhythmia: 0.12 Ventricular arrhythmia: 0.11 Inotropic infusion: 0.38
Median (IQR) length of hospital admission, days	7 (6 to 8)	7 (6 to 9)	NS
Intensive care unit > 24 hours	1 (3%)	6 (21%)	P=0.05
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The study assesses coronary artery bypass, but is still somewhat generalisable other elective surgeries.			
Applicability			
Although the trial was conducted in Denmark, it is likely to be applicable to the Australian context.			
Comments			

Abbreviations: EF, ejection fraction; CPB, cardiopulmonary bypass; OPCAB, off-pump coronary artery bypass grafting

Citation				
Goel P, Pannu H, Mohan D, and Arora R. (2007) Efficacy of cell saver in reducing homologous blood transfusions during OPCAB surgery: A prospective randomized trial. Transfusion Medicine 17:285-289.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	India / Hospital		
Intervention	Comparator			
Intraoperative cell salvage and autotransfusion of washed shed blood and transfusion of allogeneic blood if required. N=25 (although one patient was excluded from analysis)	Control: only transfused with allogeneic homologous blood. N=25			
Population characteristics				
Patients undergoing off-pump coronary artery bypass grafting.				
Length of follow-up	Outcomes measured			
NR	Transfusion frequency and volume of transfusion, haematocrit concentration, haemoglobin concentration, morbidity, mortality			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was concealed from those responsible for recruiting subjects.	The intervention groups had similar demographic characteristics.	The study was not blinded	A transfusion protocol was used.	One patient randomised to the cell saver group was excluded as he crashed on opening the left anterior descending artery and the grafting was completed on pump.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Mean (SD) volume of blood autotransfused, mL	714.8 (317.5)	NA	NA	
Mean haematocrit concentration of the autotransfused blood, %	34.6 (4.6)	NA	NA	
Patients requiring allogeneic blood transfusion	20/24 (83%)	25/25 (100%)	0.05	
Mean (SD) units of allogeneic blood transfused	1.5 (1.1)	2.4 (1.3)	P=0.02	

Mean (SD) postoperative haemoglobin concentration, g/dL	10.9 (1.5)	9.6 (0.9)	P=0.0007
Mean (SD) decrease in haemoglobin from preoperative to immediate postoperative, g/dL	1.8 (1.2)	2.7 (1.6)	P=0.02
Mortality	0/24 (0%)	0/25 (0%)	NS
Morbidity			There was no re-exploration or deep sterna wound infection in either group.
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population.			
Applicability			
The study was conducted in India, which may limit its applicability to the Australian context.			
Comments			

STUDY DETAILS				
Citation				
Mercer KG, Spark JI, Berridge DC, Kent PJ, and Scott DJA. (2004) Randomized clinical trial of intraoperative autotransfusion in surgery for abdominal aortic aneurysm. British Journal of Surgery 91:1443-1448.				
Affiliation/Source of funds				
Authors received support from The Sir Jules Thorne Charitable Trust				
Study design	Level of evidence	Location/setting		
RCT	II	UK / university hospital		
Intervention	Comparator			
Intraoperative cell salvage. Processed blood was returned to the patient as soon as haemostasis had been achieved. N=40	Control: allogeneic blood transfusion only N=41			
Population characteristics				
Patients undergoing surgery for abdominal aortic aneurysm.				
Length of follow-up	Outcomes measured			
NR (at least until hospital discharge)	Operative blood loss, patients transfused with allogeneic blood, morbidity, mortality, length of hospital stay.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was concealed from those responsible for recruiting subjects (using sealed envelopes)	The treatment groups had similar demographic characteristics.	Patients were blinded to the transfusion group allocation. Members of the operating surgical team were responsible for the continuing care of patients, decision to use blood transfusion and investigation of postoperative complications. They were independent of the research team, but were not blinded.	A transfusion protocol was used.	All analyses were conducted ITT. Four patients in the treatment arm did not receive autologous transfusion because less than 500 mL of shed blood was collected.
Overall quality assessment (descriptive)				
Good				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Median (IQR) operative blood loss, mL	1950 (775 to 285)	1270 (775 to 2850)	P=0.140	

Median (IQR) volume of salvaged blood retransfused, mL	650 (500 to 1125)	-	-
Patients transfused with allogeneic blood	21/40 (53%)	31/41 (76%)	P=0.038
Median (IQR) units of allogeneic blood transfused	1 (0 to 3)	3 (1 to 5)	P=0.012
Median (IQR) units of allogeneic and/or autologous blood transfused	3 (2 to 6)	3 (1 to 5)	P=0.783
Morbidity	SIRS: 9/40 (23%) Infection: 5/40 (13%)[1] Sepsis: 4/40 (10%)	SIRS: 20/41 (49%) Infection: 14/41 (34%)[2] Sepsis: 8/41 (20%)	*P-value* SIRS: 0.020 Infection: 0.035 Sepsis: 0.349
Mortality	1/40 (3%)[3]	1/41 (2%)	P=1.000
Median (IQR) length of hospital stay, d	12 (8 to 19)	13 (10 to 19)	P=0.385
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The study population is similar to the guideline population			
Applicability			
The results are applicable to the Australian context.			
Comments			

[1]Including four chest infections and one line infection.
[2]Including twelve chest infections, one graft infection, and one blood infection.
[3]The patient died within 30 days of surgery owing to postoperative myocardial infarction and MRSA,
[4]The patient died in hospital 37 days after surgery with pneumonia, MRSA septicaemia and acute renal failure
Abbreviations: MRSA, methicillin-resistant Staphylococcus aureus; SIRS, systemic inflammatory response syndrome

Citation				
Murphy GJ, Rogers CS, Lansdowne WB, Channon I, Alwair H, Cohen A, Caputo M, and Angelini GD. (2005) Safety, efficacy, and cost of intraoperative cell salvage and autotransfusion after off-pump coronary artery bypass surgery: A randomized trial. Journal of Thoracic and Cardiovascular Surgery 130:20-28.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence		Location/setting	
RCT	II		UK / hospital	
Intervention		Comparator		
Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the completion of the operative procedure. Salvaged washed RBCs were autotransfused at the time of skin closure. N=30		In the control group, all blood spilled, from skin incision to skin closure, was aspirated with a high-pressure sucker and discarded. N=31		
Population characteristics				
Patients scheduled for non-emergency first-time CABG (off-pump).				
Length of follow-up		Outcomes measured		
NR		Transfusion frequency, mortality, ICU length of stay, hospital length of stay, morbidity, change in haemoglobin levels.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Patients were randomised to treatment arms and allocation was concealed from those in charge of recruiting subjects.	The study groups were similar in terms of baseline characteristics	The study was not blinded.	Transfusion protocol utilised.	There was no loss to follow-up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Number of patients autotransfused, n (%)	20/30 (67%)			
Median (IQR) volume salvaged (range) / median (IQR) volume autotransfused, mL	747 (607 to 978) / 236 (206 to 342)			
Number of patients receiving any allogeneic blood product, n (%)	5/30 (17%)	11/31 (36%)	OR (95% CI): 0.36 (0.11, 1.22) P=0.095)	

Number of patients receiving homologous blood transfusion, n (%)	4/30 (13%)	7/31 (23%)	OR (95% CI): 0.53 (0.14, 2.03) P=0.35
Number of patients receiving platelet transfusion, n (%)	2/30 (7%)	6/31 (19%)	OR (95% CI): 0.30 (0.06, 1.61) P=0.26
Number of patients receiving clotting factor transfusion, n (%)	0/30 (0%)	1/31 (3%)	P>0.99
Mortality	0/30 (0%)	0/31 (0%)	P=NS
Median (IQR) length of hospital stay, d	6.0 (5.0, 8.3)	6.0 (5.0, 8.0)	OR (95% CI): 1.08 (0.65, 1.80) P=0.73
Median (IQR) length of ICU stay, d	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	OR (95% CI): 1.14 (0.67, 1.96) P=0.50
Readmission to ICU, n (%)	1/30 (3)	1/31 (3)	OR (95% CI): 1.0 (0.06, 17.32) P=0.98)
Morbidity, n (%)	Arrhythmia: 6/30 (20%) Pulmonary complications: 0/30 (0%) Stroke: 0/30 (0%) Infective complications: 2/30 (7%) Renal complications: 0/30 (0%) Myocardial infarction: 2/30 (7%)	Arrhythmia: 7/31 (23%) Pulmonary complications: 4/31 (13) Stroke: 0/31 (0%) Infective complications: 1/31 (3%) Renal complications: 2/31 (7%) Myocardial infarction: 0/31 (0%)	<u>OR (95% CI)</u> Arrhythmia: 0.86 (0.25, 2.92); P=0.81 Pulmonary complications: NA; P=0.11 Stroke: NA; P=1.0 Infective complications: NA; P=0.41 Renal complications: NA; P=0.49 Myocardial infarction: NA; P=0.24
Mean (SE) haemoglobin, g/dL	After protamine: 11.14 (0.21) 1 h: 10.55 (0.21) 24 h: 11.71 (0.21)	After protamine: 11.25 (0.21) 1 h: 10.40 (0.20) 24 h: 10.69 (0.20)	<u>Difference/ratio (95% CI)</u> After protamine: 0.11 (-0.47, 0.70) P=0.71 1 h: -0.15 (-0.74, 0.43) P=0.60 24 h: -1.02 (-1.60, 0.44) P=0.0007
Mean (SE) haematocrit, L/L	After protamine: 0.345 (0.006) 1 h: 0.312 (0.006) 24 h: 0.350 (0.006)	After protamine: 0.344 (0.006) 1 h: 0.305 (0.006) 24 h: 0.319 (0.006)	<u>Difference/ratio (95% CI)</u> After protamine: -0.001 (-0.019, 0.017) P=0.91 1 h: -0.007 (-0.024, 0.011) P=0.46 24 h: -0.031 (-0.049, -0.013) P=0.0008
Mean (SE) platelet count, $X10^9$/L	1 h: 192.8 (0.028) 24 h: 225.4 (0.027)	1 h: 189.7 (0.026) 24h: 218.2 (0.026)	

Mean (SE) prothrombin ratio	After protamine: 1.27 (0.012) 1 h: 1.19 (0.012) 24 h: 1.15 (0.012)	After protamine: 1.27 (0.012) 1 h: 1.19 (0.011) 24 h: 1.15 (0.012)	
APTT ratio	After protamine: 1.17 (0.024) 1 h: 1.08 (0.022) 24 h: 1.08 (0.022)	After protamine: 1.14 (0.022) 1 h: 1.13 (0.022) 24 h: 1.11 (0.022)	
Fibrinogen concentration, g/L	After protamine: 2.59 (0.036) 1 h: 2.21 (0.034) 24 h: 4.92 (0.035)	After protamine:2.68 (0.033) 1 h: 2.34 (0.033) 24 h:5.04 (0.034)	
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The patient population is limited to people undergoing CABG; however, the results are still somewhat generalisable to all elective non-emergency surgery with moderate blood loss.			
Applicability			
The study was conducted in the UK, however it is still applicable to the Australian context.			
Comments			

Citation				
Niranjan G, Asimakopoulos G, Karagounis A, Cockerill G, Thompson M, and Chandrasekaran V. (2006) Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on- versus off-cardiopulmonary bypass: a randomised trial. European Journal of Cardio-thoracic Surgery 30:271-277.				
Affiliation/Source of funds				
Funding from the British Heart Foundation.				
Study design	Level of evidence		Location/setting	
RCT	I		UK, hospital	
Intervention		Comparator		
Intraoperative cell salvage, with Autotransfusion of washed, salvaged red blood cells at the conclusion of the procedure. N=20 (on-pump CPB) and 20 (off-pump CPB)		Control: All lost blood from the skin incision to closure was suctioned with a high pressure sucker into a waste container. N=20 (on-pump CPB) and 20 (off-pump CPB)		
Population characteristics				
Patients undergoing first-time isolated CABG.				
Length of follow-up		Outcomes measured		
Patient followed up until discharge from hospital.		Change in haemoglobin levels, total amount of homologous blood transfusion (HBT), length of ICU stay, postoperative complications		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
The allocation was randomised and was concealed from those responsible for recruiting subjects.	The treatment groups had similar baseline characteristics.	The study was not blinded.	A transfusion protocol was utilised.	There was one death during the study in the on-CPD without cell saver group that was sudden on the pre-discharge day and attributed to an arrhythmia with no obvious cause of death found at post-mortem. The patient was included in the postoperative analysis.
Overall quality assessment (descriptive)				
Good				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Mean (SD) volume of homologous blood transfusion	On-CPB: 179 (214) Off-CPB: 141 (183) Combined: 159 (196)	On-CPB: 230 (240) Off-CPB: 595 (438) Combined: 413 (394)	Off-CPB was significantly higher than the other groups (P<0.005) Significantly lower for patients receiving cell saver (combined on-CPB and off-CPB) (p < 0.001)
Mean (SD) 24 h postoperative blood loss, mL	On-CPB: 842 (276) Off-CPB: 869 (286)	On-CPB: 1023 (291) Off-CPB: 903 (315)	P>0.05
Mean (SD) change in Hb levels from preoperative to postoperative day 1, g/dl	On-CPB: 4.95 (1.1) Off-CPB: 4.95 (1.5)	On-CPB: 4.4 (0.9) Off-CPB: 5.0 (1.6)	P>0.05
Morbidity: atrial fibrillation, n (%)	On-CPB: 7 (35) Off-CPB: 3 (25)	On-CPB: 5 (25) Off-CPB: 4 (20)	P>0.05
Morbidity: Pulmonary complications, n (%)	On-CPB: 4 (20) Off-CPB: 2 (10)	On-CPB: 3 (15) Off-CPB: 1 (5)	P>0.05
Morbidity: Renal complications, n (%)	On-CPB: 2 (10) Off-CPB: 1 (5)	On-CPB: 1 (5) Off-CPB: 0 (0)	P>0.05
Morbidity: CVA, n (%)	On-CPB: 0 (0) Off-CPB: 1 (5)	On-CPB: 1 (5) Off-CPB: 0 (0)	P>0.05
Mean (SD) length of hospital stay, d	On-CPB: 8.1 (2) Off-CPB: 7.2 (2.3)	On-CPB: 8.3 (3.1) Off-CPB: 7.4 (2.1)	P>0.05
Mean (SD) length of ICU stay, h	On-CPB: 22.1 (9.2) Off-CPB: 23 (8.4)	On-CPB: 23 (8.9) Off-CPB: 21.7 (5.8)	P>0.05
Prothrombin time			There was a significant rise on the first postoperative day from preoperative levels (P<0.0005) in all groups with no significant difference between groups. At the fifth postoperative day the PT was still elevated compared to preoperative levels in all groups with no difference between groups.
Partial thromboplastin time (ratio)			Showed a significant increase on the first postoperative day in all patient groups (P<0.001) with no significant difference between groups and was still significantly raised on the fifth postoperative day but again there was no difference between groups.

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
The study population is restricted to patients undergoing CABG; however, it is somewhat generalisable to other elective, non-emergency surgeries with moderate blood loss.	
Applicability	
The study was conducted in the UK and is likely to be applicable to the Australian context.	
Comments	

Abbreviations: CPB, cardiopulmonary bypass; CVA, cardiovascular accident

Citation				
Selo-Ojeme DO and Feyi-Waboso PA. (2007) Salvage autotransfusion versus homologous blood transfusion for ruptured ectopic pregnancy. International Journal of Gynecology and Obstetrics 96:108-111.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence		Location/setting	
RCT	II		Nigeria / University hospital	
Intervention		Comparator		
Intraoperative cell salvage with transfusion of filtered autologous blood. N=56		Control: allogeneic blood transfusion only. N=56		
Population characteristics				
Women with a diagnosis of ruptured ectopic pregnancy.				
Length of follow-up		Outcomes measured		
Follow-up up until hospital discharge.		Patients transfused with ≥ 1000 mL of blood, haematocrit concentration, morbidity, length of hospital stay		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is not clear whether allocation was concealed from those responsible for recruiting subjects.	The treatment arms had similar baseline characteristics.	The study was not blinded.	No transfusion protocol was reported.	There was no loss to follow-up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Patients transfused with ≥ 1000 mL of blood	34/56 (60%)	11/56 (20%)	RR (95% CI): 6.41 (2.75, 15.24)	
Mean postoperative haematocrit concentration, %	29%	26%	P<0.01	
Duration of surgery			"The duration of surgery was longer in the autologous group, but not significantly."	

Morbidity	Postoperative fever: 20/56 (36%) Wound infection: 3/56 (5%)	Postoperative fever: 21/56 (38%) Wound infection: 4/56 (7%)	RR (95% CI) Postoperative fever: 0.95 (0.43, 2.01) Wound infection: 0.73 (0.17, 3.19)
Mortality			"There were no deaths from ectopic pregnancies during the study period."
Patients who had a length of hospital stay of more than 7 days.	8/56 (14%)	6/56 (11%)	RR (95% CI): 1.37 (0.44, 4.31)
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The study is of women diagnosed with ruptured ectopic pregnancy and may not be generalisable to men, or people undergoing other surgery types.			
Applicability			
The study was conducted in Nigeria, which may limit its applicability in high-resource countries such as Australia.			
Comments			

Citation				
Wiefferink A, Weerwind PW, van Heerde W, Teerenstra S, Noyez L, de Pauw BE, and Brouwer RM. (2007) Autotransfusion management during and after cardiopulmonary bypass alters fibrin degradation and transfusion requirements. The Journal of extra-corporeal technology 39:66-70.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	The Netherlands / hospital		
Intervention	Comparator			
Intraoperative cell salvage: The mediastinal and residual CPB blood was processed by a continuous autotransfusion system before reinfusion. N=15	Control group: did not undergo cell salvage N=15			
Population characteristics				
Patients undergoing CABG with CPB				
Length of follow-up	Outcomes measured			
20 hours after arrival at ICU.	Number of patients transfused, length of operation			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was concealed.	The patient demographics were similar between the two groups.	The ICU staff were blinded to the group, however the surgical staff were not.	No transfusion protocol was used.	There was no loss to follow-up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Patients who received at least one unit of packed blood cells postoperatively	8/15 (54%)	10/15 (67%)	P>0.05	
Patients who received at least two units of packed blood cells postoperatively	2/15 (13%)	7/15 (47%)	P<0.05	
Mean (SD) bypass time, min	98 (25)	86 (21)	P>0.05	
Clinical importance		Clinical relevance		
EXTERNAL VALIDITY				
Generalisability				
The study population was people undergoing CPB; however, the study is likely to be somewhat generalisable for surgical procedures with moderate blood loss.				

Applicability
The study is likely to be applicable to the Australian context.
Comments

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass

Citation				
Zhang XL, Qian BH, and Luo QF. (2004) Effects of blood transfusion modes during perioperative period on prognosis of patients with scoliosis. Chinese Journal of Clinical Rehabilitation 8:7308-7310.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	China / hospital		
Intervention	Comparator			
Intraoperative cell salvage and retransfusion of washed autologous blood. N=36	Control: allogeneic transfusion only N=12			
Population characteristics				
Patients undergoing operation for scoliosis.				
Length of follow-up	Outcomes measured			
	Perioperative bleeding, patients transfused with allogeneic blood, mortality, allergic reaction			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is unclear whether allocation was concealed from those responsible for recruiting subjects.	The treatment arms had similar baseline characteristics	The study was not blinded.	No transfusion protocol was reported.	There was no loss to follow-up.
Overall quality assessment (descriptive)				
Poor				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Perioperative bleeding			"There was no difference in quantity of bleeding between the two groups."
Patients transfused with allogeneic blood	11/36 (31%)	12/12(100%)	P<0.01
Allergic reaction	0/36 (0%)	3/12 (25%)	NR
Mortality	0/36 (0%)	0/12 (0%)	-

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
The patient population were people undergoing surgery for scoliosis and may not be generalisable to other surgery types.	
Applicability	
Study was conducted in China, which may limit its applicability to the Australian context.	
Comments	

Intervention 3 – Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage

Level II evidence

Citation				
Haynes SL, Torella F, Wong JCL, Dalrymple K, James M, and McCollum CN. (2002) Economic evaluation of a randomized clinical trial of haemodilution with cell salvage in aortic surgery. British Journal of Surgery 89:731-736.				
Affiliation/Source of funds				
Funded by the NHS Executive North West Research and Developement Directorate				
Study design	Level of evidence	Location/setting		
RCT and economic analysis	II	UK / university hospital		
Intervention	Comparator			
ANH and intraoperative cell salvage n=74	Standard transfusion practice (allogeneic transfusion) n=71			
Population characteristics				
Patients undergoing aortic surgery. 34 underwent aortobifemoral bypass and 111 underwent aortic aneurysm repair.				
Length of follow-up	Outcomes measured			
	Operative blood loss, units of allogeneic blood transfused, operative time, length of hospital stay, length of ICU stay, morbidity, mortality, cost.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is not clear whether allocation was concealed from those responsible for recruiting subjects.	The study did not compare the baseline characteristics of the intervention arms.	The study was blinded.	A transfusion protocol was used.	
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Median (IQR) operative time, min	195 (162 to 238)	205 (170 to 231)	P = 0.86	
Median (range) length of ICU stay, days	1 (0 to 25)	1 (0 to 25)	P=0.89	
Mean cost of treatment[1]	£5384	£5859	NS	
Clinical importance		Clinical relevance		
EXTERNAL VALIDITY				

Generalisability
The study population is similar to the guideline population.
Applicability
The clinical outcomes are applicable to the Australian context, however the cost outcomes are not.
Comments

[1]The majority of the total cost was due to intensive care and ward stays: transfusion accounted for only 6 and 7% of the total in control and ANH + cell salvage groups respectively.

<table>
<tr><td colspan="5">Citation</td></tr>
<tr><td colspan="5">McGill N, O'Shaughnessy D, Pickering R, Herbertson M, and Gill R. (2002) Mechanical methods of reducing blood transfusion in cardiac surgery: Randomised controlled trial. British Medical Journal 324:1299-1302.</td></tr>
<tr><td colspan="5">Affiliation/Source of funds</td></tr>
<tr><td colspan="5">The study was supported by a grant from the local blood transfusion service.</td></tr>
<tr><td colspan="2">Study design</td><td colspan="2">Level of evidence</td><td>Location/setting</td></tr>
<tr><td colspan="2">RCT</td><td colspan="2">II</td><td>UK, hospital</td></tr>
<tr><td colspan="3">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="3">ANH + intraoperative cell salvage (n=86)</td><td colspan="2">1. Intraoperative cell salvage (n = 84)
2. No mechanical blood conservation, control (n = 84)</td></tr>
<tr><td colspan="5">Population characteristics</td></tr>
<tr><td colspan="5">Patients undergoing cardiac surgery.</td></tr>
<tr><td colspan="3">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="3">NR</td><td colspan="2">Transfusion frequency and dose, perioperative complications, change in haemoglobin, length of hospital stay, time in intensive care, operative time</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation</td><td>Results</td><td>Blinding analysis</td><td>Treatment/measurement bias</td><td>Follow-up (ITT)</td></tr>
<tr><td>Allocation was randomised and allocation was adequately concealed from those responsible for recruiting subjects.</td><td>The three treatment arms had similar baseline characteristics. Parsonnet scores, which reflect a number of patient variables and allow preoperative risk stratification, were also similar across the groups.</td><td>The patients, intensive care staff and trial assessors were blinded to allocation. The surgical staff could not be blinded.
Note: because the intensive care staff were blinded to allocation to group, and no protocol violations occured, it can be assumed that the reduction in allogeneic red blood cell transfusion is related to the efficacy of the treatment.</td><td>Not detected.</td><td>Two patients who were randomised could not be included because cell salvage or blood harvest machines were not available. Another two patients were excluded because of inappropriate perioperative transfusion. These four patients were not included in the analysis because of insufficient data. They were replaced with other patients in the trial who were randomised by the independent observer so that their next allocation was concealed.</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive)</td></tr>
<tr><td colspan="5">Fair</td></tr>
</table>

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Number of patients transfused with any allogeneic blood product	33/86 (38%)	Cell salvage: 32/84 (38%) Control: 47/84 (56%)	Combined treatment vs cell salvage: OR (95% CI): 1.05 (0.56, 1.98) Wald test P-value = 0.872
Number of patients transfused with allogeneic whole blood transfusion	29/86 (34%)	Cell salvage: 26/84 (31%) Control: 43/84 (51%)	Combined treatment vs cell salvage: OR (95% CI): 1.18 (0.62, 2.24) Wald test p value = 0.622
Mean (SD) units of allogeneic blood transfused per patient[1]	0.63 (1.22)	Cell salvage: 0.68 (1.55) Control: 1.07 (1.56)	Kruskal-Wallis p value = 0.015
Number of patients transfused with FFP	13/86 (15%)	Cell salvage: 14/84 (17%) Control: 13/84 (15%)	Combined treatment vs cell salvage: OR (95% CI): 0.91 (0.40, 2.11) Wald test P-value = 0.831
Mean (SD) units of FFP transfused	0.43 (1.12)	Cell salvage: 0.57 (1.47) Control: 0.49 (1.25)	Kruskal-Wallis P-value = 0.952
Number of patients transfused with platelets	15/86 (17%)	Cell salvage: 11/84 (13%) Control: 15/84 (18%)	Combined treatment vs cell salvage: OR (95% CI): 1.46 (0.62, 3.47): Wald test P-value: 0.386
Mean (SD) units of platelets transfused	0.31 (0.81)	Cell salvage: 0.20 (0.62) Control: 0.29 (0.67)	Kruskal-Wallis P-value = 0.601

Morbidity (perioperative complications)	No perioperative complications: 46/86 (53%) Inotropes required after 24 hours: 11/86 (13%) Surgical bleeding: 2/86 (2%) Cerebrovascular accident: 1/86 (1%) Arrhythmias: 20/86 (23%) Renal failure: 2/86 (2%) Proven infection: 7/86 (8%) Myocardial infarction: 4/86 (5%)	<u>Cell salvage</u> No perioperative complications: 46/84 (55%) Inotropes required after 24 hours: 12/84 (14%) Surgical bleeding: 2/84 (2%) Cerebrovascular accident: 1/84 (1%) Arrhythmias: 17/84 (20%) Renal failure: 1/84 (1%) Proven infection: 11/84 (13%) Myocardial infarction: 5/84 (6%) <u>Control</u> No perioperative complications: 42/84 (50%) Inotropes required after 24 hours: 9/84 (11%) Surgical bleeding: 3/84 (4%) Cerebrovascular accident: 2/84 (2%) Arrhythmias: 27/84 (32%) Renal failure: 0/84 (0%) Proven infection: 7/84 (8%) Myocardial infarction: 10/84 (12%)	NR
Median (IQR) haemoglobin concentration (g/l)	Before operation: 145 (138, 150) On admission to ICU: 108 (99, 116) Day 1 after operation: 105 (96, 113) Day 3 after operation: 108 (100, 119)	<u>Cell salvage</u> Before operation: 145 (136, 150) On admission to ICU: 105 (98, 116) Day 1 after operation: 104 (95, 115) Day 3 after operation: 105 (98, 115) <u>Control</u> Before operation: 142 (135, 150) On admission to ICU: 100 (91, 107) Day 1 after operation: 100 (94, 109) Day 3 after operation: 106 (98, 112)	NR
Median (IQR) length of hospital stay (h)	170.4 (147.1, 221.6)	cell salvage: 160.7 (145.5, 198.8) control: 168.9 (140.3, 219.3)	Kruskal-Wallis p-value: 0.724

Median (IQR) time in ICU (h)	23.3 (22.5, 25.0)	Cell salvage: 22.7 (22.0, 24.6) control: 22.9 (21.8, 24.5)	Kruskal-Wallis p-value: 0.249
Mean (IQR) operative time (minutes)	154 (131, 174)	Cell salvage: 160 (140, 184) control: 160 (135, 196)	NR
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
This trial was conducted on a specific patient population (people undergoing cardiac surgery), however it is likely to be generalisable to patients undergoing other elective surgical procedures with moderate blood loss.			
Applicability			
The study was performed in UK and is likely to be applicable to the Australian context			
Comments			
The combination of acute perioperative normovolaemic haemodilution and intraoperative cell salvage did not show any additional benefit over intraoperative cell salvage alone (?: check)			

[1]Nine patients needed a markedly higher amount of transfused blood (≥ 3 units). These patients were returned to the operating theatre for re-exploration of the mediastinum. A surgical cause of bleeding was found in seven of these patients (three in the control group and two each in the cell salvage and combined treatment groups).

Citation				
Wong JC, Torella F, Haynes SL, Dalrymple K, Mortimer AJ, McCollum CN, and ATIS I. (2002) Autologous versus allogeneic transfusion in aortic surgery: a multicenter randomized clinical trial. Annals of surgery 235:145-151.				
Affiliation/Source of funds				
Funded by the NHS Executive Research and Development				
Study design	Level of evidence	Location/setting		
RCT	II	UK / hospital		
Intervention	Comparator			
ANH and ICS: Before skin incision, sufficient blood was taken to reduce the haemoglobin concentration to 11 g/dL. Blood volume was replaced simultaneously with crystalloids, maintaining a steady central venous pressure during blood collection. ANH blood, containing fresh platelets and clotting factors, was retained for reinfusion at wound closure when haemostasis was secure. Blood lost during the procedure was salvaged using one of three centrifugal cell salvage devices with comparable efficacy in red cell recovery under standard conditions. All autologous blood was reinfused within 6 hours of withdrawal. N=74	Allogeneic transfusion: Patients did not receive ANH or ICS. Patients received allogeneic blood transfusion when required. N=71			
Population characteristics				
Patients undergoing aortic surgery, including 111 (59 ANH + cell salvage; 52 control) patients with aneurysms and 34 (15 ANH + cell salvage; 19 control) with occlusive disease.				
Length of follow-up	Outcomes measured			
Patients were assessed at wound closure, 2 hours, 1, 2, and 7 days after surgery.	Clinical signs, complications, transfusion requirements, and laboratory assay results.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Subjects were randomised; however, it is unclear whether allocation was censored for those responsible for recruiting subjects.	The baseline characteristics were mostly similar between the treatment arms. However, "allogeneic" patients had slightly higher mean preoperative haemoglobin concentrations (14.03 vs 13.57 g/dL; P=0.053) and ANH+cell salvage patients were slightly older (72 vs 69 years; P=0.04).	The trial was single-blind. However, the decision to give allogeneic transfusion was made by a rigid protocol and was made by a physician independent from the research team.	A transfusion protocol was used. Members of the research team attended all operations and recorded all data independently from the clinical team.	All analyses conducted ITT.

Overall quality assessment (descriptive)			
RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Mean (SD) volume of blood withdrawn during ANH, units (450 mL)	1.66 (0.71)		
Median (IQR) blood loss during surgery, mL	921 (661 to 1374)	1000 (688 to 1734)	P=0.37
Median (IQR) packed red cell volume reinfused after cell salvage, mL	415 (225 to 543)[1]	-	-
Patients requiring transfusion of allogeneic whole blood during surgery	32/74 (43%)	40/71 (56%)	P=0.12
Median (IQR) units of allogeneic blood transfused (for all patients) during surgery	0 (0 to 2)	2 (0 to 4)	P=0.008
Total units of allogeneic blood transfused	117	251	
Patients requiring transfusion of allogeneic whole blood within 24 hours of surgery	19/74 (26%)	50/71 (70%)	P<0.001
Median (IQR) units of allogeneic blood transfused (for all aneurysm patients) during surgery)	0 (0 to 2)	2 (0 to 4)	P=0.002
Total units of allogeneic blood transfused (aneurysm patients)	102	201	
Median (IQR) units of allogeneic blood transfused (for all occlusive disease patients) during surgery)	0 (0 to 2)	0 (0 to 2)	0.87
Total units of allogeneic blood transfused (occlusive disease patients)	15	50	
Mortality	13/74 (18%)	11/71 (15%)	P=0.91
Morbidity: postoperative infection	16/74 (22%)	19/71 (27%)	P=0.6
Morbidity: transfusion reaction (minor)	0/0 (0%)	1/71 (1%)	NR
Morbidity: cardiac events	13/74 (18%)	8/71 (11%)	P=0.4
Morbidity: haemorrhagic complications	5/74 (7%)[2]	8/71 (11%)[3]	NR
Reoperation	10/74 (14%)[4]	7/71 (10%)[5]	NR

Median (IQR) hospital stay, days	10 (8 to 13)	9 (7 to 12)	P=0.17
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The patient population (adults undergoing cardiac surgery) is similar to the guideline population.			
Applicability			
The study was conducted in UK, and is applicable to the Australian context.			
Comments			

[1]Equivalent to more than one unit of allogeneic blood because the haematocrit of reinfused red cells was approximately 65%.
[2]Two of the patients required a laparotomy (one for massive bleeding from the proximal aortic anastomosis, one for upper gastrointestinal haemorrhage).
[3]Three patients had intraoperative bleeding and a further five required reoperation for intra-abdominal bleeding.
[4]Five thromboembolectomies, two laparotomies for haemorrhage, two laparotomies for bowel obstruction, one groin resuturing.
[5]Five required reoperation for intra-abdominal bleeding, and two thromboembolectomies.
Abbreviations: ICS, intraoperative cell salvage

Intervention 4 – Postoperative cell salvage

Level I evidence

<table>
<tr><td colspan="5">Citation</td></tr>
<tr><td colspan="5">Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine 14:123-144.</td></tr>
<tr><td colspan="5">Affiliation/Source of funds</td></tr>
<tr><td colspan="5">The research was supported by a grant obtained from the National Health and Medical Research Council of Australia and a special purpose grant from the Hunter Area Pathology Service, Australia.</td></tr>
<tr><td colspan="2">Study design</td><td colspan="2">Level of evidence</td><td>Location/setting</td></tr>
<tr><td colspan="2">Systematic review of RCTs and observational studies with meta-analysis
Search conducted July 2002</td><td colspan="2">I</td><td>NA</td></tr>
<tr><td colspan="3">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="3">Autologous transfusion techniques: preoperative Autologous blood deposit (PAD), ANH, and cell salvage.
NOTE: This form only contains RCT info relevant for ANH.
Sample size n=704</td><td colspan="2">Comparator: no Autologous transfusion technique (active versus active comparisons were excluded).
Sample size n=591</td></tr>
<tr><td colspan="5">Population characteristics</td></tr>
<tr><td colspan="5">Patients older than 18 years undergoing any type of surgery. The mean age of participants in ANH trials was 56 years. The trials included more than twice as many males as females (2.3:1). Twelve trials involved cardiac surgery, seven involved orthopaedic surgery, and 11 involved various other operative procedures (eg, urological, thoracic, or vascular).</td></tr>
<tr><td colspan="3">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="3">NA</td><td colspan="2">Mortality, re-operation, infection, wound complication, thrombosis, non-fatal MI, rate of allogeneic red blood cell transfusion, and volume of allogeneic blood transfused.</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation</td><td>Results</td><td>Blinding analysis</td><td>Treatment/measurement bias</td><td>Follow-up (ITT)</td></tr>
<tr><td>Allocation concealment and the method of randomisation were judged by the SR authors to be inadequate in 100 and 92% of trials respectively (kappa=0.78-1.0).</td><td>SR did not discuss similarity between preoperative data and baseline characteristics for the intervention groups.</td><td>The majority (96%) of the included RCTs assessing ANH were unblended.</td><td>Not detected</td><td>NR</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive)</td></tr>
</table>

Fair			
RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Mortality 8 trials (n=NR)	NR	NR	RR (95% CI): 1.16 (0.19, 7.15) P*het*=NR
Morbidity: infection 2 trials (n=NR)	NR	NR	RR (95% CI): 4.94 (0.61, 40.19) P*het*=NR
Morbidity: thrombosis 3 trials (n=NR)	NR	NR	RR (95% CI): 0.44 (0.21, 0.93) P*het*=NR
Morbidity: non-fatal MI 3 trials (n=NR)	NR	NR	RR (95% CI): 3.43 (0.15, 79.74) P*het*=NR
Re-operation 7 trials (n=NR)	NR	NR	RR (95% CI):1.59 (0.20, 12.53) P*het*=NR
Rate of allogeneic blood transfusion: all studies 25 trials (n=1081; 567 ANH, 514 control)	273/567 (48%)	357/514 (69%)	RR (95% CI): (P*het*<0.00001)
Rate of allogeneic blood transfusion: cardiac surgery 10 trials (n=NR)	NR	NR	RR (95% CI): 0.77 (0.57, 1.04)
Rate of allogeneic blood transfusion: orthopaedic surgery 6 trials (n=NR)	NR	NR	RR (95% CI): 0.79 (0.60, 1.06)
Rate of allogeneic blood transfusion: miscellaneous surgery 9 trials (n=NR)	NR	NR	RR (95% CI): 0.42 (0.24, 0.74)
Rate of allogeneic blood transfusion: transfusion protocol used 16 trials (n=NR)	NR	NR	RR (95% CI): 0.81 (0.62, 1.00)
Rate of allogeneic blood transfusion: transfusion protocol not used/reported 9 trials (n=NR)	NR	NR	RR (95% CI): 0.53 (0.36, 0.76)
Difference in units of allogeneic blood transfused 17 trials	NR	NR	WMD (95% CI) Overall: -1.9 (-1.1, -2.7) Studies with a transfusion protocol: -1.0 (-1.7, -0.4) Studies without a transfusion protocol: -3.0 (-4.9, -1.1)

Hospital length of stay, d 3 trials (N=96)	NR	NR	WMD (95% CI): 0.21 (-1.26, 1.68)
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population			
Applicability			
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).			
Comments			

Abbreviations: ANH, acute normovolemic haemodilution; MI, myocardial infarction; PAD, preoperative autologous donation; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; WMD, weighted mean difference.

Citation				
Carless PA, Henry DA, Moxey AJ, O'connell DL, Brown T, and Fergusson DA. (2006) Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane database of reviews; Issue 4.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR Search conducted Jan 2004	I	NA		
Intervention	Comparator			
Cell salvage. Studies with a combination of active comparisons were included if both the intervention and control groups were equally exposed to the active treatment (ie, active plus cell salvage versus active comparisons). N (perioperative cell salvage) = 1952 The authors found 51 studies.	Any N=1905			
Population characteristics				
Adults (over 18 years) undergoing elective, non-urgent surgery. Surgery types found in the search include cardiac (23 studies), orthopaedic (23 studies), and vascular (5 studies) surgery. 33 of the trials studied cell salvage during the postoperative period, 10 studied intraoperative cell salvage, and seven studied both intraoperative and postoperative cell salvage. One trial failed to describe the timing of cell salvage. Twenty trials studied cell salvage systems that reinfused washed salvaged blood, and 29 trials studied cell salvage systems that reinfused unwashed filtered salvaged blood. One trial studied both washed and unwashed cell salvage (4-arm trial) and provided two comparisons of cell salvage.				
Length of follow-up	Outcomes measured			
NA	Number of patients transfused with allogeneic and/or autologous blood, amounts of allogeneic and/or autologous blood transfused, re-operation for bleeding, postoperative complications, mortality, and length of hospital stay.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
According to the authors, the description of the method to conceal allocation of either inadequate or unclear for all of the studies.	-	Based on the Schulz criteria, blinding was reported in only one of the trials.	Nine of the 51 studies did not report a transfusion protocol.	-
Overall quality assessment (descriptive)				
Good				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Rate of allogeneic transfusion (postoperative cell salvage) 16 trials (n=NR)			RR (95% CI): 0.58 (0.43, 0.79) P*het*=NR
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The SR is generalisable for elective, non urgent surgery.			
Applicability			
The studies were mostly from countries with similar health-care systems to Australia			
Comments			
The systematic review includes trials assessing the intraoperative, postoperative, and both intra- and postoperative. There is more data but most of it combines intra- and postoperative data.			

Abbreviations: RR, relative risk; ARR, absolute risk reduction; RRR, relative risk reduction

Citation		
Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, and McCollum C. (2006) Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: A systematic review and economic model. Health Technology Assessment 10:1-114.		
Affiliation/Source of funds		
One author received sponsorship from haemonetics and AstraTech to attend the International Society of Blood Transfusion (ISBT) VIIIth European Congress. The author has also given invited lectures for AstraTech Ltd and Unomedical with honoraria and expenses paid.		
Study design	Level of evidence	Location/setting
SR with economic analysis (SR search is an update of Carless 2003: a Cochrane review that had been updated in 2006. The study includes a meta-analysis combining the results of Carless 2003 and the search update. Search conducted Jan 2004	I	NA
Intervention	Comparator	
Transfusion strategies to minimise perioperative allogeneic blood transfusion: cell salvage, PAD, PAD plus EPO, EPO, ANH, cell salvage plus ANH, AFs, FSs, restrictive transfusion thresholds or protocols. NB: This form only includes information relevant for postoperative cell salvage. <u>Specific characteristics of the 1 included RCT (Naumenko 2003)</u> Drainage discharge collected for 8 hours postoperatively and reinfused. Erythrocytes reinfused postoperatively after washing. NB: the authors of the SR were not able obtain a full version of Naumenko 2003, and therefore had to rely on information provided in the abstract.	No cell salvage or allogeneic blood.	
Population characteristics		
For inclusion, the SRs had to only include adults undergoing elective, non-urgent surgery. <u>Specific characteristics of the 1 included RCT (Naumenko 2003)</u> Patients undergoing CABG surgery		
Length of follow-up	Outcomes measured	
NA	Proportion/number of patients transfused with allogeneic and/or autologous blood; the volume of allogeneic and/or autologous blood transfused; reoperation for bleeding; adverse transfusion reactions; preoperative morbidity and Hb levels; postoperative complications; length of hospital stay; mortality.	

INTERNAL VALIDITY[1]				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Method of randomisation not described and allocation concealment unclear.	Naumenko 2003 had unclear baseline comparability: 'no significant difference between groups was detected at any stage of the study'	Did not have participant blinding and it is unclear whether study had allocation concealment.	The abstract of Naumenko 2003 does not describe the use of a transfusion protocol.	Unclear intention to treat (however there was no loss to follow-up).
Overall quality assessment (descriptive)				
Good				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Number of patients transfused with allogeneic blood (postoperative cell salvage; active versus control[2])	287/738 (39%)	473/724 (65%)	RR (95% CI): 0.60 (0.45, 0.79) P<0.05	
Clinical importance		Clinical relevance		
EXTERNAL VALIDITY				
Generalisability				
The review includes all surgery types and performs subgroup analyses by surgery type. Therefore the results are likely to be generalisable for other elective, non-emergency operations.				
Applicability				
Transfusion frequency outcome: Good applicability Other outcomes - poor applicability to the question - With the exception of transfusion frequency, all of the outcomes assessed combined data from intra- and postoperative cell salvage.				
Comments				
The updated lit search included 2 RCTs (1 as abstract only): Naumenko 2003 and Zhao 2003. Zhao 2003 investigated intraoperative cell salvage (described in this form), and Naumenko 2003 investigated postoperative cell salvage (described in I4). The SR includes a meta-analysis using data from the above two trials, as well as the data from Carless 2003 (a Cochrane review that had been updated in 2006. Except for transfusion frequency, all of the outcomes meta-analysed combined trials using intra- and postoperative cell salvage.				

[1]Refers only to the one intraoperative cell salvage RCT included in the systematic update (Zhao 2003)

Citation				
Duffy G and Neal KR. (1996) Differences in postoperative infection rates between patients receiving autologous and allogeneic blood transfusion: a meta-analysis of published randomized and nonrandomized studies (Structured abstract). Transfusion Medicine 6:325-328.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR of RCTs and retrospective studies Search date NR	I	NA		
Intervention	Comparator			
Autologous transfusion (including PAD or cell salvage)	Allogeneic blood transfusion only			
Population characteristics				
Length of follow-up	Outcomes measured			
Patients undergoing any surgical operation.	Infections.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
NR	Baseline characteristics NR	NR	SR did not define whether a transfusion protocol was used	NR
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Infection (1 trial)	1/35 (3%)	3/35 (9%)	OR (95% CI): 3.2 (0.4, 29.0)	
Clinical importance		Clinical relevance		
EXTERNAL VALIDITY				
Generalisability				
Limited generalisability (due to uncertainty regarding the small sample size, and lack of info regarding potential sources of bias).				
Applicability				
The SR does not report the location of the Newman 1995 trial.				
Comments				
NB: only one postoperative cell salvage RCT included (Newman 1995)				

Citation				
Huet C, Salmi R, Fergusson D, Koopman-Van Gemert AWMM, Rubens F, and Laupacis A. (1999) A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. Anesthesia and Analgesia 89:861-869.				
Affiliation/Source of funds				
Coordinating Centre has been funded by Janssen Ortho Inc, Canada. One of the authors is the recipient of the First Fellowship from the International Society of Technology Assessment in Health Care, funded by the PPP Medical Trust.				
Study design	Level of evidence	Location/setting		
SR of RCTS with Meta-analysis Search conducted December 1997	I	NA		
Intervention	Comparator			
Perioperative cell salvage				
Population characteristics				
Patients who underwent cardiac or orthopaedic surgery (two articles dealing with vascular surgery were not considered).				
Length of follow-up	Outcomes measured			
NA	Proportion of patients receiving at least one unit of allogeneic packed red blood cells			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Three of the included trials were pseudo-randomised.		Unclear: "all of the 28 trials included in this study scored between zero and three on the Jadad scale. Because it is difficult to "blind" the operative team to the presence or absence of cell salvage, the Jadad score would rarely be expected to be greater than 3"	The SR did not report on whether or not a transfusion protocol was used in the RCTs	NR
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Patients transfused with allogeneic blood (active versus: CABG surgery using washed salvage (active vs control analysis) 6 trials (n=482; 246 cell salvage, 236 control)			RR: 0.84 (95% CI: 0.77, 0.93) P<0.05 (P*het*=NR)	

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
The review includes all surgery types and performs subgroup analyses by surgery type. Therefore the results are likely to be generalisable for other elective, non-emergency operations.	
Applicability	
Low applicability to the question - all of the outcomes assessed combined data from intra- and postoperative cell salvage.	
Comments	
27 references, representing 28 RCTs, were included in the meta-analysis. NB: The authors did not separately analyse intra- and postoperative cell salvage; however, all of the cardiac surgery trials used postoperative cell salvage. See section I2 for the perioperative cell salvage values for orthopaedic surgery, and other outcomes not assessed in a specific postoperative population.	

[1] Includes both studies where an active treatment is compared with a control intervention and those studies where both the intervention and control arms also received an additional active intervention (c.f. active versus control, where the controls are untreated).

Level II evidence

Citation				
Amin A, Watson A, Mangwani J, Nawabi D, Ahluwalia R, and Loeffler M. (2008) A prospective randomised controlled trial of autologous retransfusion in total knee replacement. Journal of Bone and Joint - Series B 90:451-454.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence		Location/setting	
RCT	II		UK / Hospital	
Intervention		Comparator		
Postoperative cell salvage: The tourniquet was released before closure and one deep drain was inserted within the joint space. The drain was connected either to the Bellovac ABT Autotransfusion system. The shed blood was returned to the patient after collecting up to 500 mL and no later than six hours after surgery. A maximum of 1200 mL was retransfused. N=92		Control: The drain was connected to a standard vacuum chamber, and the collected blood was discarded. N=86		
Population characteristics				
Patients undergoing unilateral TKA. All patients aged over 55 years with osteoarthritis and/or inflammatory arthritis of the knee.				
Length of follow-up		Outcomes measured		
NR		Transfusion (%), transfusion (vol), haemoglobin concentration, morbidity, length of hospital stay		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was concealed	The study and control groups had similar patient demographics.	Not blinded	A transfusion protocol was used.	There were eight patients who were not retransfused.[1] These patients were included in the study based on an 'intention to treat' principle.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Mean (SD) change in haemoglobin, g/dL	2.2 (0.7)	2.6 (0.8)	P=0.354	
Patients transfused with allogeneic blood	12/92 (13%)	13/86 (15%)	P=0.439	
Total units of blood transfused	22	26	NR	
Median (IQR) drainage volume, mL	659 (100 to 1900)	638 (86 to 1470)	P=0.468	

Median (IQR) of autologous blood retransferred, mL	481 (200 to 1110)	NA	NA
Morbidity	Wound infection: 3/92 (3%) DVT: 1/92 (1%) Persistent wound drainage (no infection): 2/92 (2%) Other infections: 2/92 (2%) Returns to operating theatre: 1/92 (1%)	Wound infection: 2/86 (2%) DVT:2/86 (2%) Persistent wound drainage (no infection): 1/86 (1%) Other infections: 2/86 (2%) Returns to operating theatre: 0/86 (0%)	NS
Median (IQR) length of hospital stay, days	6.6 (3 to 14)	7.0 (3 to 16)	P=0.54
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The study population is generalisable for elective surgery with moderate blood loss			
Applicability			
Study is applicable to the Australian context.			
Comments			

[1]Five patients were not retransfused because of low drainage volumes (< 100 mL) and three patients who were not retransfused because of technical difficulties such as problems with the tubing and filter system.

Citation				
Cheng SC, Hung TS, and Tse PY. (2005) Investigation of the use of drained blood reinfusion after total knee arthroplasty: a prospective randomised controlled study. Journal of orthopaedic surgery (Hong Kong) 13:120-124.				
Affiliation/Source of funds				
Sponsored by the Tung Wah Group of Hospitals Research Fund.				
Study design	Level of evidence	Location/setting		
RCT	II	Hong Kong / Hospital		
Intervention	Comparator			
Postoperative cell salvage: patients in the reinfusion group had their blood reinfused from drains within 6 hours of surgery. N=26	Control: Shed blood was not reinfused. N=34			
Population characteristics				
Patients undergoing knee arthroplasty				
Length of follow-up	Outcomes measured			
3 days post-surgery	Patients requiring allogeneic transfusion, units of allogeneic transfusion, mean haemoglobin level, total operative blood loss, reinfusion volume, febrile complications.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Subjects were randomised into intervention groups. Allocation was concealed from those responsible for recruiting subjects.	The control group had a larger proportion of patients with a pre-morbid condition (65% vs 54%) and a larger proportion of males compared with the reinfusion group (35% vs 23%). However, these differences were not significant.	Near the end of each operation, the corresponding envelope for each patient was opened, and the surgeon was informed at the time of drain insertion to achieve a single-blind effect.	Transfusion protocol implemented.	There was no loss to follow-up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Median (IQR) total operative blood loss, mL	273 (100 to 600)	280 (100 to 800)	P=0.84
Median (IQR) reinfusion volume, mL	425.2 (180 to 620)	NA	NA
Patients requiring allogeneic transfusion	4/26 (15%)	13/34 (38%)	P=0.05

Median (IQR) units of allogeneic transfusion	0.15 (0 to 1)	0.46 (0 to 4)	P=0.033
Median haemoglobin level (IQR), g/L	Immediately postoperative: 101 (84 to 128) Day 3: 98 (77 to 130)	Immediately postoperative: 104 (87 to 137) Day 3: 101 (77 to 130)	P-value Immediately postoperative: 0.332 Day 3: 0.401
Febrile complications	2/26 (8%)	1/34 (3%)	P=0.403
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The patients in the study were specifically undergoing total knee arthroplasty; however the study is generalisable to other elective, non-emergency surgery types associated with moderate blood loss.			
Applicability			
The study was conducted in Hong Kong; however, it is likely to be applicable to the Australian context.			
Comments			

Citation				
Zacharopoulos A, Apostolopoulos A, and Kyriakidis A. (2007) The effectiveness of reinfusion after total knee replacement. A prospective randomised controlled study. International Orthopaedics 31:303-308.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
RCT	II	Greece, hospital		
Intervention	Comparator			
Postoperative cell salvage and reinfusion of washed blood within 6 hours of operation. N=30	Control: banked blood unit was given intraoperatively, and a standard wound drainage system was used. N=30			
Population characteristics				
Patients undergoing total knee replacement. There were 47 female and 13 male patients with a mean age of 69.7 years.				
Length of follow-up	Outcomes measured			
15 days postoperative	Intra- and postoperative blood loss, volume of unwashed blood salvage returned, number of autologous blood transfusions, perioperative haemoglobin values, operation time, length of hospital stay.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation concealment was not reported	Patient demographics were not reported.	The study was not blinded.	A transfusion protocol was not used.	It is unclear whether all patients randomised were included in the analyses.
Overall quality assessment (descriptive)				
Poor				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
"Average"[1] (range) volume of blood reinfused, mL	808 (300 to 1750)		
Mean volume of homologous blood transfused, units	0.3	1.5	NR
Patients requiring postoperative homologous blood transfusion	5/30 (16.6%)	10/30 (33.3%)	NR
Difference in haemoglobin and haematocrit			NS

Clinical importance	Clinical relevance
EXTERNAL VALIDITY	
Generalisability	
The patients were restricted to those undergoing total knee replacement; however, the study is generalisable for elective, non-emergency surgery associated with moderate blood loss.	
Applicability	
The study was conducted in a hospital situated in a small town of 8000 inhabitants. This may limit the applicability to larger hospitals.	
Comments	

[1]The authors report some results as "average" without explicitly stating whether they are referring to mean or median.

Intervention 5 – Deliberate induced hypotension

Level I evidence

Citation		
Paul JE, Ling E, Lalonde C, Thabane L. Deliberate hypotension in orthopedic surgery reduces blood loss and transfusion requirements: A meta-analysis of randomized controlled trials. Canadian Journal of Anaesthesia 2007;54(10):799-810.		
Affiliation/Source of funds		
Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada. Funding: Hamilton Health Sciences, Department of Anesthesia Academic Fund.		
Study design	Level of evidence	Location/setting
Systematic review including 17 RCTs that investigated the effects of deliberate hypotension on blood loss and transfusion requirements in patients undergoing orthopaedic surgery.	Level I	Hospital

Intervention	Comparator
Deliberate hypotension by any method	No deliberate hypotension
Population characteristics	
Patients undergoing orthopaedic surgery	
Length of follow-up	Outcomes measured
NR	Intraoperative blood loss, transfusion requirements, duration of surgery

INTERNAL VALIDITY

Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all studies. Method of randomisation not reported.	Baseline characteristics of intervention and control groups not reported. A random effects model was use in the mate-analyses as the test of heterogeneity was significant (p<0.05).	One was a double blinded study. Six were single blinded studies. Ten were open-labelled studies.	Egger's test for bias was non-significant (p=0.955), suggesting that there was no publication bias. Data extraction for each study was performed independently by the three authors. Consensus between reviewers was considered good with a kappa score of 0.87.	No lost to follow-up in all studies

Overall quality assessment (descriptive)

Good. This review clearly defined the research question, scope, search terms and inclusion/exclusion criteria. The search strategy employed appeared robust, and the methods for analysis were appropriate. The summary, as well as a quality rating, for each included study was provided. This review provided pooled data, for each of the specified outcomes, through meta-analysis of the data from included studies.

RESULTS

Outcome	Intervention group	Comparator group	Statistical significance
Blood loss	NR	NR	-286 mL (95%CI : -447, -127)
Transfusion requirements	NR	NR	-667 mL (95%CI : -963, -370)

Surgery duration	NR	NR	-1.9 min (95%CI : -7.2, 3.5)
Outcome	Clinical importance	Clinical relevance	
Blood loss	1: reduced blood loss	1	
Transfusion requirements	1: reduced requirements	1	
Surgery duration	4	2	
EXTERNAL VALIDITY			
Generalisability			
This systematic review focus on patients undergoing orthopaedic surgery, which may not share clinical characteristics with the general surgical patient population.			
Applicability			
The studies in this review were mostly conducted in developed countries (mostly European), comparable to Australia. The surgeries performed (and the possible benefits) are likely applicable in Australia.			
Comments			
This review suggests that induced hypotension may decrease blood loss, transfusion requirement and surgery duration.			

Abbreviations: CI, confidence intervals; NR, not reported; RCTs, randomised controlled trials.

Level II evidence

Citation				
Boldt J, Weber A, Mailer K, Papsdorf M, Schuster P. Acute normovolaemic haemodilution vs controlled hypotension for reducing the use of allogeneic blood in patients undergoing radical prostatectomy. British Journal of Anaesthesia1999;82(2):170-174.				
Affiliation/Source of funds				
Department of Anaesthesiology and Intensive Care Medicine and the Clinic of Urology, Klinikum der Stadt Ludwigshafen, Bremserstr, Germany. Funding: NR				
Study design	Level of evidence		Location/setting	
RCT	Level II		Hospital	
Intervention		Comparator		
Controlled hypotension (MAP: 50mm Hg) using sodium nitroprusside Controlled hypotension with haemodilution (beyond the scope of Q3:Intervention 5)		No induced hypotension		
Population characteristics				
40 patients, under the age of 75 years undergoing retropubic radical prostatectomy with bilateral pelvic lymphadenectomy. Exclusion criteria: ASA class IV, myocardial infarction within 6 months, documented coronary artery disease or carotid artery stenosis, abnormal coagulation, liver dysfunction, medication with aspirin, renal insufficiency.				
Length of follow-up		Outcomes measured		
Up to the first postoperative day in the ward		Blood loss, transfusion dose and frequency, coagulation status		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomisation using blinded envelopes	No significant differences in patient clinical characteristics were observed between the intervention and control group	Blinded envelopes used. Postoperative administration of blood/blood products provided by an independent physician blinded to patient's study group.	All patients operated on by one of two surgical teams. Postoperative administration of blood/blood products provided by an independent physician blinded to patient's study group.	No death or lost to follow-up
Overall quality assessment (descriptive)				
Good. This RCT provides clear description for the research question and methods. The analyses performed were appropriate and the results presented clearly.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	1260 (SD: 570)	1920 (SD: 590)	P<0.05
Transfusion frequency	25%	60%	P<0.05
Total transfusion dose in group (units)	14	28	P<0.05
Coagulation status	NR	NR	No significant difference
Cost per patient (blood, volume replacement, intervention)	US$82.81	US$139.99	P<0.05

Outcome	Clinical importance	Clinical relevance
Blood loss	1: reduced blood loss	1
Transfusion frequency	1: reduced frequency	1
Transfusion dose	1: reduced requirements	1
Coagulation status	4	1
Cost per patient	NA	NA
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted on a specific patient population (males with ASA status I-III, undergoing retropubic radical prostatectomy with bilateral pelvic lymphadenectomy, in addition to several other exclusion criteria). Consequently, the findings of this study may not be applicable to other surgical patient populations.		
Applicability		
This trial was conducted in Germany, with a developed healthcare system comparable to that in Australia. As such the findings of the study are applicable.		
Comments		
This study shows that induced hypotension reduces blood loss, costs, transfusion dose and frequency.		

Abbreviations: ASA, American Society of Anaesthesiologists physical status; MAP, mean arterial pressure; NA, not applicable; NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive anaesthesia. British Journal of Anaesthesia 2006;96(6):727-731.				
Affiliation/Source of funds				
Faculty of Medicine, Ain-shams University, Cairo, Egypt. Funding: NR				
Study design	Level of evidence	Location/setting		
Double-blinded RCT	Level II	Hospital		
Intervention	Comparator			
Magnesium sulphate induced hypotension	No induced hypotension			
Population characteristics				
60 patients undergoing functional endoscopic sinuses surgery.				
Length of follow-up	Outcomes measured			
NR, includes postoperative monitoring	Blood loss, surgery duration			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised, computerized random allocation.	No significant differences in patient clinical characteristics were observed between the intervention and control group	Double –blinded. Anaesthetist was unaware of the patients' treatment group.	Intraoperative bleeding was evaluated by the same surgeon every 15 minutes	No subjects excluded
Overall quality assessment (descriptive)				
Good. This RCT provided a clear description of its research scope and methods. The statistical analyses were appropriate and presented well. However, it does not provide an assessment/discussion of possible limitations or bias in this study.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Blood loss (mL)	165 (SD: 19)	257 (SD: 21)	P<0.05	
Surgery duration (minutes)	68 (SD: 15)	88 (SD: 10)	P<0.001	
Outcome	Clinical importance	Clinical relevance		
Blood loss	1: reduced blood loss	1		
Surgery duration	1: reduced duration	2		
EXTERNAL VALIDITY				
Generalisability				
This RCT was conducted on a specific patient population (patients undergoing functional endoscopic sinuses surgery). Consequently, the findings of this study may not be applicable to other surgical patient populations.				
Applicability				
This trial was conducted in Egypt, which likely has comparable healthcare facilities to Australia. As endoscopic sinuses surgeries are performed in Australia, this study is likely applicable.				
Comments				

This study shows that magnesium sulphate induced hypotension reduces intraoperative blood loss and surgery duration.

Abbreviations: NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Fredin H, Gustafson C, Rosberg B. Hypotensive anesthesia, thromboprophylaxis and postoperative thromboembolism in total hip arthroplasty. Acta Anaesthesiologica Scandinavica 1984;28(5):503-507.				
Affiliation/Source of funds				
Department of Anaesthesiology and Orthopaedic Surgery. Malmo General Hospital, Sweden. Funding: Swedish National Association against Heart and Chest Diseases and Herman Jarnhardt's Foundation.				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Induced hypotension using sodium nitroprusside (systolic blood pressure: 70-80mm Hg) with low-dose heparin and dihydroergotamine (HDHE)	No induced hypotension with HDHE			
Population characteristics				
57 patients undergoing total hip arthroplasty. Exclusion criteria: Patients with cardiovascular, pulmonary, renal, hepatic or thyroid diseases.				
Length of follow-up	Outcomes measured			
10-14 days after surgery	Blood loss, transfusion dose, incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE).			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Method NR	No significant differences in patient clinical characteristics were observed between the intervention and control group	Patient blinding NR. Diagnosis of DVT and PE were re-evaluated by an independent specialist, who were blinded to the patients' treatment status	NR	8 subjects with revision arthroplasties were excluded from study and not included in analysis
Overall quality assessment (descriptive)				
Fair. This RCT provides clear description for the research question and scope. However, it is lacking details regarding the randomisation and blinding procedure. Statistical analyses performed were appropriate and well presented. Discussion did not assess possible biases in the study.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Intraoperative blood loss (mL)	620 (SD: 240)	1070 (SD: 630)	P<0.001
Total blood loss (mL)	1170 (SD: 395)	1700 (SD: 860)	P<0.01
Intraoperative transfusion dose (mL)	580 (SD: 390)	1210 (SD: 620)	P<0.01
Total transfusion dose (mL)	920 (SD: 580)	1540 (SD: 1050)	P<0.01
Incidence of DVT	11/24	10/26	Not significant
Incidence of PE	6/26	1/28	Not significant

Outcome	Clinical importance	Clinical relevance
Peroperative blood loss	1: reduced blood loss	1
Total blood loss	1: reduced blood loss	1
Peroperative transfusion dose	1: reduced transfusion dose	1
Total transfusion dose	1: reduced transfusion dose	1
Incidence of DVT	4	1
Incidence of PE	4	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted on a specific patient population (patients undergoing Hip Arthroplasty, in addition to several other exclusion criteria). Consequently, their clinical characteristics may differ from a general surgery patient population.		
Applicability		
This trial was conducted in Sweden, with a similarly developed healthcare system as Australia. However, it is important to note that as this study was conducted in 1983, changes to patient management or clinical practice may affect the applicability of this study.		
Comments		
This study shows that induce hypotension reduces blood loss, transfusion dose.		

Abbreviations: DVT, deep vein thrombosis; HDHE, low-dose heparin and dihydroergotamine; NR, not reported; PE, pulmonary embolism; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Jacobi KE, Bohm BE, Rickauer AJ, Jacobi C. Moderate controlled hypotension with sodium nitroprusside does not improve surgical conditions or decrease blood loss in endoscopic sinus surgery. Journal of Clinical Anaesthesia 2000;12(3):202-207.				
Affiliation/Source of funds				
University of Erlangen-Nuremberg, Erlangen, Germany.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Hospital	
Intervention		Comparator		
Moderate hypotension (MAP: 65–75mmHg) using sodium nitroprusside		No induced hypotension		
Population characteristics				
32 patients undergoing endoscopic sinus surgery (ASA class I and II)				
Length of follow-up	Outcomes measured			
3 hours post-operation	Blood loss			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised via computer generated random numbers.	No significant differences in patient clinical characteristics, duration of anaesthesia, intraoperative treatment were observed between the intervention and control group	NR	Hypotension group received same treatment as control group, plus sodium nitroprusside.	No lost to follow-up
Overall quality assessment (descriptive)				
Fair. This study did not include a description of the blinding methods employed, if any.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	278 ± 110	245 ± 132	P>0.05
Outcome	Clinical importance	Clinical relevance	
Blood loss	4	1	
EXTERNAL VALIDITY			
Generalisability			
This RCT was conducted on a specific patient population (patients undergoing endoscopic sinus surgery, ASA class I and II). Consequently, the findings of this study may not be applicable to other surgical patient populations.			
Applicability			
This trial was conducted in Germany, with a similarly developed healthcare system as Australia. As such the findings of the study may be relevant in the Australian context.			
Comments			
The authors suggest that moderate hypotension may not be effective in reducing blood loss, while other studies suggest that profound hypotension (MAP=50mmHg) can provide a reduction in blood loss during surgery.			

Abbreviations: ASA, American Society of Anaesthesiologists physical status; MAP, mean arterial pressure; NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Karakaya D, Ustun E, Tur A, Baris S, Sarihasan B, Sahinoglu H, Guldogus F. Acute normovolemic hemodilution and nitroglycerin-induced hypotension: Comparative effects on tissue oxygenation and allogeneic blood transfusion requirement in total hip arthroplasty. Journal of Clinical Anesthesia 1999;11(5):368-374.				
Affiliation/Source of funds				
Ondokuz Mayis University, Kurupelit-SAMSUN, Turkey. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Nitroglycerine induced hypotension (60–65 mmHg)	No induced hypotension			
Population characteristics				
20 ASA class I and II patients undergoing primary total hip arthroplasty, performed via the posterior approach in the lateral decubitus position.				
Length of follow-up	Outcomes measured			
Up to fifth postoperative day	Surgery duration, transfusion requirements, haemoglobin level.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised. Method NR.	No significant differences in patient clinical characteristics were observed between the intervention and control group	NR	All surgeries performed by a single surgeon. Subjects with bleeding disorders not included in study.	No lost to follow-up.
Overall quality assessment (descriptive)				
Fair. This RCT did not describe the blinding method employed, if any. Due to the small sample size in each group, non-parametric methods should have been used.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Surgery duration (minutes)	171.0 (SD: 26.6)	163.5 (SD: 24.9)	P>0.05
Blood transfusion (units)	2.3 (SD: 0.8)	2.7 (SD: 1.1)	P>0.05
Haemoglobin (g/dL) 5 minutes after intubation End of operation Fifth postoperative day	 11.6 (SD: 0.4) 9.2 (SD: 0.19) 10.2 (SD: 0.3)	 11.9 (SD: 0.8) 9.7 (SD: 0.2) 10.3 (SD: 0.5)	 P>0.05
Outcome	Clinical importance	Clinical relevance	
Surgery duration	4	2	
Blood transfusion	4	1	
Haemoglobin	4	1	

EXTERNAL VALIDITY
Generalisability
This RCT was conducted on a specific patient population (ASA status I and II, undergoing hip arthroplasty, in addition to several other exclusion criteria). Consequently, the findings of this study may not be generalisable to other surgical patient populations.
Applicability
This trial was conducted in Turkey. Possible differences in the healthcare system, in addition to the small sample size make it difficult to assess the applicability in the Australian context.
Comments

Abbreviations: ASA, American Society of Anaesthesiologists physical status; NR, not reported; RCT, randomised clinical trial.

Citation				
Kop EC, Spauwen PHM, Kouwenberg PPGM, Heymans FJM, van Beem HBH. Influence of controlled hypotension versus normotension on amount of blood loss during breast reduction. Journal of Plastic, Reconstructive and Aesthetic Surgery 2009;62(2):200-205.				
Affiliation/Source of funds				
University Medical Centre, Nijmegen, Netherlands. Slingeland Hospital, Doetinchem, Netherlands. Funding: Article was not supported by any funds.				
Study design	Level of evidence	Location/setting		
Double-blinded RCT	Level II	Hospital		
Intervention	Comparator			
Controlled hypotension using nitroprusside (MAP: 50mmHg)	Normotension			
Population characteristics				
85 Patients (<60 years, ASA I and II) undergoing bilateral breast reduction surgery. Other Exclusion criteria: diabetes, hypertension, coagulation disturbances, kidney or liver dysfunction.				
Length of follow-up	Outcomes measured			
6 weeks post-operation	Blood loss			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Random selection of envelope assigning patient to treatment group	No significant differences in patient clinical characteristics were observed between the intervention and control group	Double-blinded. Only anaesthesiologist knew the patients' treatment group.	Surgeon, who was unaware of patient's treatment group, determined when perfusor was stopped. Anaesthesiologist was not involved in data analysis.	34 patients did not meet selection criteria. Excluded from analysis.
Overall quality assessment (descriptive)				
Good. This RCT provided a clear description of the research scope and study methods. The discussion included an assessment of possible limitations such as the in the measurement of intraoperative blood loss.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	316 (Range: 133–560)	598 (Range (250–1335)	P<0.001
Surgery duration (minutes)	56.4 (Range: 41–73)	62.7 (Range: 48–78)	P=0.013
Outcome	Clinical importance	Clinical relevance	
Blood loss	1: Reduced blood loss	1	
Surgery duration	1: Reduced surgery duration	2	

EXTERNAL VALIDITY
Generalisability
This RCT was conducted on a specific patient population (females with ASA status I-II under the age of 60, undergoing bilateral breast reduction, in addition to several other exclusion criteria). Consequently, the findings of this study may not be applicable to other surgical patient populations.
Applicability
This trial was conducted in the Netherlands, which is similarly well developed like Australia. As this surgical procedure is performed in Australia, the findings of this study is likely applicable.
Comments
This study shows that induced hypotension reduces blood loss and surgery duration during breast reduction surgery

Abbreviations: ASA, American Society of Anaesthesiologists physical status; MAP, mean arterial pressure; NR, not reported; RCT, randomised clinical trial.

Citation				
O'Connor PJ, Hanson J, Finucane BT. Induced hypotension with epidural/general anesthesia reduces transfusion in radical prostate surgery. Canadian Journal of Anesthesia 2006;53(9):873-880.				
Affiliation/Source of funds				
University of Alberta, and the Division of Health, Population and Information, Cross Cancer Institute, Edmonton, Alberta, Canada.				
Study design	Level of evidence	Location/setting		
Prospective, randomised, single-blind trial	Level II	University of Alberta Hospital, Canada		
Intervention	Comparator			
Combined epidural and anaesthesia to control mean arterial pressure (MAP) at 50-60mmHg.	General anaesthesia alone, no control of MAP.			
Population characteristics				
99 patients, ASA status I-III, with adenocarcinoma of the prostate to undergo radical retropubic prostatectomy.				
Length of follow-up	Outcomes measured			
Patients monitored up till discharge.	Primary outcome: Blood loss, transfusion frequency and dose. Secondary outcome: Operating time, hospital length of stay, occurrence of serious adverse events.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomisation using a computer-generated table of random numbers, patients were block randomised (block size=10) using blinded study envelopes which were opened prior to surgery.	No significant differences in patient clinical characteristics were observed between the intervention and control group	Single-blinded.	The lack of blinding of the anaesthesiologists involved. The use of rigid automatic laboratory-based transfusion trigger could introduce potential bias due to the effects of haemodilution. However, the trigger rates in the intervention and control group were comparable.	NR
Overall quality assessment (descriptive)				
Good. This RCT provides clear description for the randomisation, inclusion and exclusion criteria, methods, outcomes measured, and employed suitable statistical methods for analysis. The discussion was comprehensive and assessed possible limitations and biases. Anaesthesiologists were not blinded, however, only 23% of the transfusions were decided by the anaesthesiologist. The remaining 77% of transfusions were initiated postoperatively by non-study personnel.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	955 (SD: 517)	1477 (SD: 823)	*P*<0.001
Transfusion frequency	2/49 (4%)	9/50 (18%)	*P*=0.028
Total transfusion dose in group (units)	3	24	NR
Operating time (minutes)	107 (SD:36)	122 (SD:32)	*P*=0.038

Hospital length of stay (>5 days)	24/49 (49%)	34/50 (68%)	*P*=0.055
Serious adverse events	0	0	NA
Outcome	Clinical importance	Clinical relevance	
Blood loss	1: reduced loss	1	
Transfusion requirements	1: reduced requirements	1	
Mean transfusion dose	NA	1	
Operating time	2: reduced duration	2	
Hospital length of stay	4	1	
Serious adverse events	NA	1	
EXTERNAL VALIDITY			
Generalisability			
This RCT was conducted on a specific patient population (males with ASA status I-III, with adenocarcinoma of the prostate, undergoing radical retropubic prostatectomy and bilateral pelvic lymphadenectomy). Consequently, the findings of this study may not be applicable to other surgical patient populations (e.g. females, patients with ASA status III-V).			
Applicability			
This trial was conducted in Canada, with a similarly developed healthcare system as Australia. As such the findings of the study may be relevant in the Australian context.			
Comments			
This study shows that induce hypotension reduces blood loss, transfusion frequency and operating time.			

Abbreviations: ASA, American Society of Anaesthesiologists physical status; MAP, mean arterial pressure; NA, not applicable; NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Piper SN, Suttner SW, Maleck WH, Kumle B, Haisch G, Boldt J. Effects of sodium nitroprusside-induced controlled hypotension on pancreatic function assessed by pancreatitis-associated protein in patients undergoing radical prostatectomy. European Journal of Anaesthesiology 2002;19(8):609-613.				
Affiliation/Source of funds				
Department of Anaesthesiology and Intensive Care Medicine, Klinikum Ludwigshafen, Germany. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Controlled hypotension (MAP: 50mm Hg) using sodium nitroprusside	No induced hypotension			
Population characteristics				
30 patients undergoing elective radical prostatectomy (ASA class II and III only)				
Length of follow-up	Outcomes measured			
24 hours post-operation	Blood loss, blood transfusion dose, duration of surgery			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised using a random list.	No significant differences in patient clinical characteristics were observed between the intervention and control group	NR	Routine intraoperative care used for both study groups.	No lost to follow-up
Overall quality assessment (descriptive)				
Fair. This study did not include a description of the blinding methods employed, if any. Also, as the primary aim of this study was not blood loss/transfusion, the authors did not discuss these outcomes in detail.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	843 (SD: 233)	1526 (SD: 409)	P<0.05
Transfusion frequency	0 patients	4 patients	P<0.05
Total transfusion dose in group (units)	0	10	P<0.05
Surgery duration (minutes)	154 (SD: 20.6)	164 (SD: 20.6)	P>0.05
Haemoglobin concentration	Higher in intervention group than control group		P<0.05
Outcome	Clinical importance	Clinical relevance	
Blood loss	1:reduced blood loss	1	
Transfusion frequency	1: reduced frequency	2	
Transfusion dose	1: reduced requirements	2	
Surgery duration	4	2	

Haemoglobin concentration	1:Increased haemoglobin concentration	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted on a specific patient population (males with ASA status II-III, undergoing radical prostatectomy, in addition to several other exclusion criteria). Consequently, the findings of this study may not be applicable to other surgical patient populations.		
Applicability		
This trial was conducted in Germany, with a similarly developed healthcare system as Australia. As such the findings of the study may be relevant in the Australian context.		
Comments		
This study shows that induced hypotension reduces blood loss and blood transfusion.		

Abbreviations: ASA, American Society of Anaesthesiologists physical status; MAP, mean arterial pressure; NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Sood S, Jayalaxmi TS, Vijayaraghavan S, Nundy S. Use of sodium nitroprusside induced hypotensive anaesthesia for reducing blood loss in patients undergoing lienorenal shunts for portal hypertension. British Journal of Surgery 1987;74(11):1036-1038.				
Affiliation/Source of funds				
All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Sodium nitroprusside induced hypotensive anaesthesia (systolic blood pressure < 95mmHg)	No induced hypotension			
Population characteristics				
18 patients undergoing elective, proximal, lienorenal shunts for portal hypertension.				
Length of follow-up	Outcomes measured			
48 hours after surgery	Blood loss, transfusion dose.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised using table of random numbers.	Control group had more males and more subjects with extrahepatic obstruction.	NR	Preoperative investigations, surgical technique and postoperative management were undertaken by the same surgical and anaesthetic teams for both treatment groups.	2 patients were excluded, not considered in analysis.
Overall quality assessment (descriptive)				
Fair. This RCT did not provide a clear description for the blinding methods used, if any. The study also provides no assessment/discussion of possible limitations or bias. The final study sample size of 18 patients is small, however statistical significance was achieved in the analysis.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	517 (SD: 220)	1286 (SD: 523)	P<0.01
Transfusion requirement (units)	0.88 (SD: 0.9)	3.0 (SD: 1.2)	P<0.01
Outcome	Clinical importance	Clinical relevance	
Blood loss	1: reduced blood loss	1	
Transfusion requirement	1: reduced requirements	1	
EXTERNAL VALIDITY			
Generalisability			
This RCT was conducted on a specific patient population (patients undergoing elective, proximal, lienorenal shunts for portal hypertension). In addition, the small sample size makes it difficult for findings of this study to be extended to the general surgical population.			
Applicability			

This trial was conducted in India, in a large well-established medical institution. As such the level and quality of healthcare is likely comparable to that in Australia. As such the findings of this study are likely applicable.
Comments
This study shows that sodium nitroprusside induced hypotension blood loss and transfusion requirements.

Abbreviations: NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Suttner SW, Piper SN, Lang K, Huttner I, Kumle B, Boldt J. Cerebral effects and blood sparing efficiency of sodium nitroprusside-induced hypotension alone and in combination with acute normovolaemic haemodilution. British Journal of Anaesthesia 2001;87(5):699-705.				
Affiliation/Source of funds				
Department of Anaesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Germany. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Controlled hypotension (MAP: 50mm Hg) using sodium nitroprusside Controlled hypotension with haemodilution (beyond the scope of Q3:Intervention 5)	No induced hypotension			
Population characteristics				
28 patients, undergoing elective radical prostatectomy. Exclusion criteria: ASA class greater than III, myocardial infarction within 6 months, documented coronary artery disease or carotid artery stenosis, abnormal coagulation, liver dysfunction, medication with aspirin, renal insufficiency.				
Length of follow-up	Outcomes measured			
Up to discharge from post anaesthesia care unit	Blood loss, transfusion dose and frequency.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised, method not specified.	No significant differences in patient clinical characteristics were observed between the intervention and control group	NR	Anaesthesiologist was not involved in data analysis.	6 subjects failed to meet inclusion criteria, excluded from analysis
Overall quality assessment (descriptive)				
Good. This RCT included a modest number of subjects, although initial power calculations suggest that the study was sufficiently powered. Information as to the method of randomising and blinding was not specified. The analyses performed were appropriate and the results presented clearly.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	788 (SD: 193)	1335 (SD: 460)	P<0.05
Transfusion frequency	1/14 (7%)	7/14 (50%)	P<0.05
Total transfusion dose in group (units)	3	17	P<0.05
Outcome	Clinical importance	Clinical relevance	
Blood loss	1: reduced blood loss	1	
Transfusion frequency	1: reduced frequency	1	
Transfusion dose	1: reduced requirements	1	
EXTERNAL VALIDITY			

Generalisability
This RCT was conducted on a specific patient population (males with ASA status I-III, undergoing radical prostatectomy, in addition to several other exclusion criteria). Consequently, the findings of this study may not be applicable to other surgical patient populations.
Applicability
This trial was conducted in Germany, with a comparable level of healthcare as in Australia. As such the findings of the study are likely applicable.
Comments
This study shows that induced hypotension reduces blood loss, transfusion dose and frequency.

Abbreviations: ASA, American Society of Anaesthesiologists physical status; MAP, mean arterial pressure; NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Intervention 6 – Prevention of hypothermia

Level I evidence

Citation		
Mahoney CB, Odom J. Maintaining intraoperative normothermia: a meta-analysis of outcomes with costs (Structured abstract). AANA J 1999;67:155-164.		
Affiliation/Source of funds		
Carlson School of Management, University of Minnesota. Funding: NR		
Study design	Level of evidence	Location/setting
Meta-analysis of 18 studies to determine the difference in patients' outcomes between normothermic and mildly hypothermic patients undergoing surgery.	Level I	Hospitals

Intervention	Comparator
Maintenance of normothermia	Mild hypothermia

Population characteristics
Studies which include patients undergoing any surgery. Patient population does not include cases of extreme hypothermia.

Length of follow-up	Outcomes measured
NR. Appears variable, with only some studies providing information on length of stay.	Transfusion dose and frequency, mortality rate, myocardial infarction, cost, length of stay in hospital and ICU

INTERNAL VALIDITY

Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
3 of the 18 included studies were not randomised. Method NR.	The authors state that there were no significant differences in the general characteristics between the intervention and control group, in any of the included studies.	NR	Possible sources of bias were addressed by statistical adjustment during meta-analysis, where information was available. Publication bias of the meta-analysis was not reported.	NR

Overall quality assessment (descriptive)
Poor. The literature search conducted in this meta-analysis is acceptable. However, the inclusion of non-randomised trials (3/18) and the lack of information on the allocation method and blinding of individual studies diminish the quality of this study. The meta-analysis explored possible sources of bias and provided useful estimates for several outcomes of interest.

RESULTS

Outcome	Intervention group	Comparator group	Statistical significance
Units of red blood cells transfused	0.117 (SD: 0.0247)	1.167 (SD: 0.0867)	P<0.05
Units of plasma transfused	0.3 (0.09)	1.4 (0.2)	P<0.05
Units of platelets transfused	0.2 (0.01)	0.9 (0.06)	P<0.05
Need for transfusion (probability)	14.43% (SD: 3.14)	24.19% (SD: 4.57)	P<0.05

Length of stay (days)	11.77 (SD: 0.1047)	19.44 (SD: 0.1600)	P<0.05
Time in ICU (hours)	5.51 (SD: 0.0863)	9.70 (SD: 0.1712)	P<0.05
Myocardial infarction (probability)	2.30% (SD: 0.88)	4.07% (SD: 1.34)	P<0.05
Mortality (probability)	2.70% (SD: 0.85)	6.01% (SD: 1.73)	P<0.05
Cost savings	Between $2495–$7073 per patient		NA
Outcome	Clinical importance	Clinical relevance	
Units of red blood cells transfused	1	1	
Units of plasma transfused	1	1	
Units of platelets transfused	1	1	
Need for transfusion	1	1	
Length of stay	1	2	
Time in ICU	1	1	
Myocardial infarction	1	1	
Mortality	1	1	
Cost savings	NA	NA	
EXTERNAL VALIDITY			
Generalisability			
This review included studies of patients undergoing a variety of surgical procedures, in which several methods of hypothermia prevention were used. The maintenance of normothermia had a positive effect across a number of clinically important outcomes, as such, is likely to be beneficial in part to the general surgical population (excluding extreme hypothermia cases).			
Applicability			
The studies were conducted in developed countries (similar to Australia). The surgical procedures included are relevant in the Australian context. As such, this intervention and its findings are likely to be applicable in Australia.			
Comments			
This review suggests that the maintenance of normothermia results in fewer adverse outcomes, and lower overall hospital cost.			

Abbreviations: ICU, intensive care unit; NA, not applicable; NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. Anesthesiology 2008;108(1):71-77.				
Affiliation/Source of funds				
Department of Outcomes Research, Cleveland Clinic, Cleveland Ohio. Funding: National Institutes of Health Grant and the Joseph Drown Foundation.				
Study design	Level of evidence	Location/setting		
Systematic review of 18 RCTs that compared normothermic patients to those who had mild intraoperative hypothermia.	Level I	Hospitals		
Intervention	Comparator			
Maintenance of normothermia	Mild hypothermia (34–36°C)			
Population characteristics				
Studies which include patients undergoing any surgery. Patient population does not include studies where the core temperature is less than 34°C.				
Length of follow-up	Outcomes measured			
NR.	Blood loss and need for blood transfusion.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
All included studies were randomised. Method NR.	Analysis of baseline characteristics of each study not reported.	NR	Funnel plots used did not indicate substantial publication bias for either outcome. No significant study effect on treatment effect size observed.	ITT was specified in 10 studies.
Overall quality assessment (descriptive)				
Good. This review clearly defined the research question and strategy. Although detailed characteristics of included studies were absent, quality scores were assigned for each study. The statistical analyses were well conducted and clearly presented. The presences of publication bias and study effect were also examined.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (Intervention vs control)	NR	NR	Ratio: 0.84 (0.74, 0.96)
Need for transfusion	NR	NR	RR=0.78 (0.63, 0.97)
Outcome	Clinical importance	Clinical relevance	
Blood loss	2	1	
Need for transfusion	2	1	

EXTERNAL VALIDITY
Generalisability
This review included studies of patients undergoing a variety of surgical procedures. However, this review excluded studies where the core temperature was less than 34°C, or if hypothermia had been induced. As such, the patient population may not be representative of patients undergoing surgery in which cooling methods are employed.
Applicability
The studies were conducted in developed countries (similar to Australia). The surgical procedures included are relevant in the Australian context. As such, this intervention and its findings are likely applicable in Australia.
Comments
This review suggests that the maintenance of normothermia results in less blood loss, and a reduced need for blood transfusions.

Abbreviations: NR, not reported; RCT, randomised clinical trial; RR, relative risk; SD, standard deviation.

Citation				
Scott EM, Buckland R. A systematic review of intraoperative warming to prevent postoperative complications (Structured abstract). AORN Journal 2006;83:1090-1104.				
Affiliation/Source of funds				
University of Durham, Stockton-on-Tees, England. Easington Primary Care Trust, Country Durham, England. Funding: Actamed ltd, Wester Yorkshire, UK, and Pegasus ltd, Hampshire, UK.				
Study design	Level of evidence	Location/setting		
Systematic review of 26 RCTs that examined if preventing hypothermia during surgery prevents postoperative complications such as need for blood transfusion.	Level I	Hospitals		
Intervention	Comparator			
Prevention of hypothermia during surgery	No prevention of hypothermia.			
Population characteristics				
Patients having surgical procedures (other than cardiac procedures) under regional or general anaesthesia.				
Length of follow-up	Outcomes measured			
NR, studies must include follow-up beyond intraoperative phase (ie during the post-anesthesia care unit, or hospital stay).	Need for blood transfusion, morbid cardiac events (eg myocardial infarction, angina, tachycardia) and pain.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
All included studies were randomised. NR in 13 studies. 6 studies used computer generated numbers for allocation. 4 used sealed opaque envelopes. 1 used sealed envelopes. 1 used flip of a coin. 1 used random number generator blocking every 10 patients.	Baseline characteristics of intervention and control groups were comparable all except two studies, where the age and weight differed between treatment and control groups. All except three studies showed significant differences in the temperature between the treatment and control group.	8 studies were double-blinded. 8 studies were single-blinded. 8 studies NR. 2 studies stated blinding not possible.	Publication bias or bias of individual studies not reported.	NR
Overall quality assessment (descriptive)				
Fair. This review provides clear description for the randomisation, inclusion and exclusion criteria, and quality assessment of the included studies. However, the pooled estimates for morbid cardiac events were derived from just two studies, while the need for blood transfusion was derived from four studies. No assessment of publication bias was performed.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Morbid cardiac events	NR	NR	RR=0.34 (0.20, 0.57)
Need for blood transfusion (yes/no)	NR	NR	RR=0.39 (0.22, 0.68)
Pain	No significant differences in pain between groups		
Outcome	Clinical importance	Clinical relevance	
Morbid cardiac events	1: reduced risk	1	
Need for blood transfusion	1: reduced need for transfusion	1	
Pain	4	1	
EXTERNAL VALIDITY			
Generalisability			
This review included studies of patients undergoing a variety of surgical procedures, in which several methods of hypothermia prevention were used. The review excluded studies involving cardiac procedures; as such it may not be representative of cardiac surgery patients.			
Applicability			
The studies in this review were not conducted in Australia; however, they were conducted in developed countries with similarly developed healthcare systems.			
Comments			
This review suggests that preventing hypothermia during surgery may reduce the likelihood of morbid cardiac events and the need for blood transfusion.			

Abbreviations: NR, not reported; RCT, randomised clinical trial; RR, relative risk.

Citation				
Jeong SM, Hahm KD, Jeong YB, Yang HS, Choi IC. Warming of intravenous fluids prevents hypothermia during off-pump coronary artery bypass graft surgery. Journal of Cardiothoracic and Vascular Anesthesia 2008;22:67-70.				
Affiliation/Source of funds				
University of Ulsan, Seoul Korea. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Warmed (41°C) intravenous fluids	Conventional treatment			
Population characteristics				
40 patients undergoing isolated off-pump coronary artery bypass (OPCAB) surgery.				
Length of follow-up	Outcomes measured			
Biochemical measurements, up to 24 hours after operation.	Blood transfusion dose, surgery duration, temperature, ICU stay, hospital stay.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Method NR.	No difference in preoperative characteristics between patient groups.	Investigators not blinded	Standardised treatment and management applied to all subjects irrespective of treatment group.	No lost to follow-up.
Overall quality assessment (descriptive)				
Poor. The authors recognise that the small sample size was likely underpowered to detect changes in clinical data, as the study was designed to be powered to detect a change in patient temperature. Investigators were not blinded the treatment group of the subjects, this may have led to bias.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood transfusion dose (mL)	400.5 ± 622.8	365.0 ± 437.1	P>0.05
Surgery duration (minutes)	247 ± 59	245 ± 49	P>0.05
Bladder temperature at 4 hours into operation (°C)	36.6 ± 0.32	35.8 ± 0.7	P<0.05
ICU stay (hours)	59.6 ± 19.6	70.5 ± 17.8	P>0.05
Hospital stay (days)	10.6 ± 2.2	11.6 ± 2.7	P>0.05
Outcome	Clinical importance	Clinical relevance	
Blood loss	4	1	
Surgery duration	4	2	
Bladder temperature	1: higher temperature	1	

ICU stay	4	2
Hospital stay	4	2
EXTERNAL VALIDITY		
Generalisability		
The small sample size of this study, and the specific patient population examined (patients undergoing OPCAB) makes generalising the findings from this study difficult.		
Applicability		
This study was conducted in Korea. Differences in the level of healthcare between Korea and Australia may limit the applicability of the findings of this study.		
Comments		
Warming of intravenous fluids does not reduce blood loss, ICU stay or hospital stay in patients undergoing OPCAB.		

Abbreviations: NR, not reported; OPCAB, off-pump coronary artery bypass; RCT, randomised clinical trial.

Citation			
Kim YS, Lee JY, Yang SC, Song JH, Koh HS, Park WK. Comparative Study of the Influence of Room-Temperature and Warmed Fluid Irrigation on Body Temperature in Arthroscopic Shoulder Surgery. Arthroscopy – Journal of Arthroscopic and Related Surgery 2009;25(1):24-29.			
Affiliation/Source of funds			
College of Medicine, Catholic University of Korea, Seoul, Korea. The Armed Forces Capital Hospital, Korea. Funding: NR			
Study design	Level of evidence	Location/setting	
RCT	Level II	Hospital	
Intervention	Comparator		
Warm irrigation fluid (35–37°C)	Irrigation fluid at room temperature		
Population characteristics			
50 ASA I or II patients undergoing arthroscopic shoulder surgery.			
Length of follow-up	Outcomes measured		
1 days post-operation	Change in haemoglobin, surgery duration, pain, hypothermia, body temperature		
INTERNAL VALIDITY			
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Method NR.	No difference in preoperative characteristics between patient groups.	Postoperative measurements were recorded by an independent observer blinded to the study.	All operative procedures were performed by the same orthopaedic surgeon.	Four patients exclude because of incomplete data. Excluded from analysis
Overall quality assessment (descriptive)			
Fair. This RCT had clearly defined research questions and methods. Based on the results of previous studies, their power calculation indicated that they had over 80% power.			

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Change in Haemoglobin (g/dL)	1.7 ± 0.7	1.4 ± 0.6	P=0.165
Surgery duration (minutes)	94.5 ± 21.9	91.1 ± 32.4	P=0.68
Postoperative pain (VAS)	5.0 ± 1.7	4.9 ± 1.6	P=0.927
Final body temperature (°C)	36.2 ± 0.3	35.5 ± 0.3	P<0.001
Hypothermia (%)	17.4	91.3	P<0.001
Outcome	Clinical importance	Clinical relevance	
Change in Haemoglobin	4	1	
Surgery duration	4	2	
Postoperative pain	4	1	

Hypothermia	1: reduced incidence of hypothermia	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted in a specific patient population (undergoing arthroscopic shoulder surgery). As such, they may not share clinical characteristics with a general surgical patient population.		
Applicability		
This study was conducted in a military hospital in Korea. Differences in the demographics and exposure of the patients and the level of healthcare, as compared to Australia may limit the applicability of the findings of this study.		
Comments		
This review suggests that the warm fluid irrigation reduces perioperative hypothermia, however it does not significantly influence the change haemoglobin following surgery.		

Abbreviations: NR, not reported; RCT, randomised clinical trial; VAS, visual analogue scale.

Citation				
Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: A randomised controlled trial. Lancet 2001;358(9285):876-880.				
Affiliation/Source of funds				
University Hospital of North Tees, Stockton-on-Tees, UK. Funding: Action Research and Smith & Nephew Foundation.				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Preoperative warming	Standard care (no preoperative warming)			
Population characteristics				
421 patients having clean surgery (breast, varicose vein, or hernia), that would result in a scar longer than 3 cm. Exclusion criteria: Pregnant, under 18 years, long term steroids, had received radiotherapy or chemotherapy in the last 4 weeks, or had an infection at the time of the surgery.				
Length of follow-up	Outcomes measured			
6 weeks	Wound infection, ASEPSIS score.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Method NR.	No difference in preoperative characteristics between patient groups.	Treatment allocation concealed in opaque envelopes.	A single train observer, blinded to the treatment allocation assessed subjects at 2 and 6 weeks for wound infection.	6 patients lost to follow-up at 6 weeks. Outcomes evaluated on an ITT basis.
Overall quality assessment (descriptive)				
Good. Prospective power calculations indicated that the sample size provided 90% power to detect a 5% change in infection rates. Statistical analyses performed were appropriate, with multivariate analysis used to identify possible risk factors.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Wound infection	13 (5%)	19 (14%)	P=0.001
ASEPSIS score 0–10 11–20 21–30 31–40 >40	 259 (94%) 8 (3%) 6 (2%) 2 (0.7%) 2 (0.7%)	 115 (83%) 7 (5%) 9 (7%) 6 (4%) 2 (1%)	P=0.007
Outcome	Clinical importance	Clinical relevance	
Wound infection	1	1	
ASEPSIS	1	2	

EXTERNAL VALIDITY
Generalisability
This RCT was conducted in patients undergoing a variety of clean surgery, as such findings of this study may be generalisable to other surgical patients undergoing similar clean surgeries. The study was adequately powered, adding credibility to the study findings.
Applicability
This study was conducted in the UK, which has a similar healthcare system to Australia. Also, the surgical procedures examined are performed in Australia, as such, findings from this study are likely applicable in Australia.
Comments
This study suggests that preoperative warming reduces the incidence of wound infection in patients undergoing clean surgical procedures.

Abbreviations: RCT, randomised clinical trial.

Citation				
Yau TM, Carson S, Weisel RD, Ivanov J, Sun Z, Yu R, Glynn MF, Teasdale SJ. The effect of warm heart surgery on postoperative bleeding. The Journal of Thoracic and Cardiovascular Surgery 1992;103:1155-1162.				
Affiliation/Source of funds				
The Toronto Hospital and the University of Toronto, Toronto, Ontario, Canada. Funding: Medical Research Council of Canada				
Study design	Level of evidence	Location/setting		
Double-blinded RCT.	Level II	Hospital		
Intervention	Comparator			
Warm systemic perfusion (35–37°C)	System perfusion at 25–29°C			
Population characteristics				
146 consecutive patients undergoing isolated primary coronary artery bypass grafting (CABG).				
Length of follow-up	Outcomes measured			
Up to six days after operation	Blood loss, transfusion requirements, haemoglobin levels.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation reported using a randomisation table.	No difference in preoperative characteristics between patient groups.	Patient and surgeon blinded to the treatment group.	Transfusion of blood ordered by surgeon or anaesthetist who was not aware of the patient's treatment group.	Three patients who had reoperation were excluded from analysis.
Overall quality assessment (descriptive)				
Fair. This double-blinded RCT has clearly defined research questions, with several post-operation follow-up carried out. Antifibrinolytic therapy was concurrently used by some patients in this study, and was not controlled for in this study; however, the use of such therapy had no bearing on the assignment to treatment group and as such would have had a non-differential effect, if any. The authors recognised that their sample size may have been underpowered to detect differences between treatment groups.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Post operative blood loss : 6 hours 12 hours 24 hours	 409 ± 36 mL 591 ± 38 mL 864 ± 42 mL	 418 ± 41 mL 596 ± 50 mL 918 ± 68 mL	 P>0.05
Blood transfusion frequency	55%	64%	P=0.24
Haemoglobin levels	NR	NR	P>0.05

Outcome	Clinical importance	Clinical relevance
Blood loss at 6 hours	4	1
Blood loss at 12 hours	4	1
Blood loss at 24 hours	4	1

Blood transfusion frequency	4	1
Haemoglobin levels	4	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted in a specific patient population (undergoing CABG surgery). As such, they may not share clinical characteristics with a general surgical patient population. In addition, the small sample size and the resulting lack of power, as recognised by the authors, make it difficult to draw conclusions with any certainty.		
Applicability		
This study was conducted in Canada, which has comparable healthcare system. CABG surgeries are regularly performed in Australia. As such, these findings may have some relevance to a similar patient population in Australia.		
Comments		
This review suggests that the use of warm system perfusion during heart surgery does not reduce postoperative bleeding.		

Abbreviations: CABG, coronary artery bypass grafting; NR, not reported; RCT, randomised clinical trial.

Citation				
Zhao J, Luo AL, Xu L, Huang YG. Forced-air warming and fluid warming minimize core hypothermia during abdominal surgery. Chinese medical sciences journal / Chinese Academy of Medical Sciences 2005;20:261-264.				
Affiliation/Source of funds				
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Warming with air-forced warming blanket and intravenous fluid warming system	Conventional treatment (Covered in cotton sheet)			
Population characteristics				
40 patients undergoing abdominal surgery lasting at least 2 hours (ASA class I and II).				
Length of follow-up	Outcomes measured			
NR	Blood loss, surgery duration, red blood cell transfusion, plasma transfusion and core temperature.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Method NR.	No difference in preoperative characteristics between patient groups.	NR	Standardised treatment and management applied to all subjects irrespective of treatment group.	No lost to follow-up.
Overall quality assessment (descriptive)				
Fair. This RCT did not provide a description of the blinding or randomisation methods employed.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Blood loss (mL)	639 (SD: 441)	421 (SD: 249)	P>0.05
Surgery duration (minutes)	204 (SD: 76)	230 (SD: 88)	P>0.05
Red blood cell transfusion (units)	2.6 (SD: 2.5)	1.6 (SD: 2.4)	P>0.05
Plasma transfusion (units)	220 (SD: 460)	240 (SD: 480)	P>0.05
Core temperature (°C)	36.4 (SD: 0.4)	35.3 (SD: 0.5)	P<0.001

Outcome	Clinical importance	Clinical relevance
Blood loss	4	1
Surgery duration	4	2
Red blood cell transfusion	4	1
Plasma transfusion	4	1
Core temperature	1: increased temperature	1

EXTERNAL VALIDITY
Generalisability
This study examined patients undergoing selective abdominal surgery (ASA Class I and II), as such it is likely most generalisable to patients undergoing such surgical procedures.
Applicability
This study was conducted in China, which has a different healthcare system and demographics to Australia. As such, it is difficult to assess the applicability and feasibility of such an intervention in Australia.
Comments
This study found that warming prevents hypothermia during abdominal surgery; however, no significant effect was observed on blood loss and transfusion requirements.

Abbreviations: ASA, American Society of Anaesthesiologists; NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Intervention 7 – Point-of-care testing using thromboelastography

Level II evidence

<table>
<tr><td colspan="3">Citation</td></tr>
<tr><td colspan="3">Ak, K., Isbir, SC., et al., Thromboblastography-based algorithm reduces blood product use after elective CABG: a prospective randomised study. Journal of Cardiac Surgery 2009;24:404-410.</td></tr>
<tr><td colspan="3">Affiliation/Source of funds</td></tr>
<tr><td colspan="3">Department of Cardiovascular Surgery, Marmara University, Istanbul, Turkey
Department of Biochemistry, Marmara University, Istanbul, Turkey
Cardiovascular Surgery Unit, Academic Hospital, Istanbul, Turkey
No conflict of interest</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location/setting</td></tr>
<tr><td>Prospective RCT
Randomisation process not described</td><td>II</td><td>Turkey, Academic hospital.</td></tr>
<tr><td colspan="2">Intervention</td><td>Comparator</td></tr>
<tr><td colspan="2">Thromoboelastography (TEG) based algorithm guided transfusion (N=114) (comprising kaolin-activated (k) TEG and h-kTEG analyses) which was a modified version of the one proposed by Royston and Kier[6] using tranexamic acid instead of aprotinin.</td><td>Clinician-directed transfusion (CDT, n=110) using criteria obtained from abnormal conventional laboratory tests (PT, APTT and platelet count) absence of visible clots and presence of generalized oozing-type bleeding in the surgical field to determine blood product administration.</td></tr>
<tr><td colspan="3">Population characteristics</td></tr>
<tr><td colspan="3">224 patients undergoing elective first-time coronary artery bypass grafting (CABG) with cardiopulmonary bypass.
For CDT and TEG respectively: mean ages 65.9 and 63.2, males 79% and 75%, diabetes mellitus 35% and 29%.
Additional treatment: 65% of CDT group and 59% of TEG group on aspirin therapy prior to the operation Additional doses of protamine sulphate were given to some patients Transamine 10% initial dose was given at 10mg/kg over 20 mins followed by an infusion of 1mg/(kg.h) PRBCs transfused when hemocrit>25% (18% during CPB) –if patient was intolerant to anaemia or older age the threshold for blood transfusion was raised.</td></tr>
<tr><td colspan="2">Length of follow-up</td><td>Outcomes measured</td></tr>
</table>

[6] Royston, D., von Kier S. Reduced hemostatic factor transfusion during heparinise-modified thromboelstaography during cardiopulmonary by-pass. Br J Anaesth 2001;86:575-578.

Not specified but at least 30 days after the operation.	Outcomes measured • Transfusion • Early mortality (death within 30 days of the operation) Outcomes were measured at 6 time points: T1= Before induction of general anaesthesia T2=After institution of CPB T3=15 mins after the administration of protamine suphate T4=On admission to the intensive care unit T5=6 hours after CPB T6=24 hours after CPB

INTERNAL VALIDITY

Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Random	No significant difference between groups in demographics and perioperative variables but hypertension was significantly higher in the TEG group - 13% vs. 32%, P=0.000.	Anaesthesiologist performing transfusion was blinded to the patient's group assignment (It is not clear how important this blinding was i.e. did this person also assesses the need for transfusion). It is not clear if the clinician directing transfusion or assessing other interventions was aware of the study group the patient belonged to.	There was the possibility of measurement bias as the two groups did not have the same coagulation tests which may have been advantageous to the TEG group. There was also the possibility of assessment bias.	All patients were included in the analyses. Transfusion requirements measured until discharge (LOS=6.2-6.3 days). Patient status followed up for at least 30 days post operation.

Overall quality assessment (descriptive)

Fair

RESULTS

Outcome	Intervention group Thromoboelastography (TEG) (kTEG & h-kTEG assays) N=114	Comparator group Clinician directed transfusion (CDT) (tests=PT, aPTT, platelets) N=110	Statistical significance
Mean (SD) mediastinal chest tube drainage, mL	480.5 (351)	591.4 (339.2)	P=0.087
Early mortality (defined as death within 30 days of operation)	3 patients (2.7%) (low cardiac output=2, multiple organ failure=1)	2 patients (1.7%) (mediastinitis=1, respiratory insufficiency=1)	Not reported
Clinical importance Reported by Authors as 'no difference'		Clinical relevance 1	
Re-exploration for bleeding	6 patients (causes all surgical)	5 patients (Causes, 2= surgical, 3 inappropriate surgical intervention for bleeding)	Not reported

Clinical importance Reported by Authors as 'no difference'		Clinical relevance 1	
Patients transfused with PRBC	52/114 (45.6%)	60/110 (54.5%)	P=0.181
Patients transfused with FFP	19/114 (16.6%)	31/110 (28.1%)	P=0.038
Patients transfused with platelets	17/114 (14.9%)	29/110 (26.3%)	P=0.033
Median (IQR) units of PRBCs transfused intraoperatively	1 (0, 1)	0 (0, 1)	P=0.581
Median (IQR) units of PRBCs transfused postoperatively	1 (0, 1)	1 (0, 1)	P=0.741
Median (IQR) units of PRBCs transfused both intra-and postoperatively	1 (0, 1)	1 (1, 2)	P=0.599
Clinical importance 3		Clinical relevance 1	
Median (IQR) units of FFP transfused intraoperatively	0 (0, 1)	1 (0, 1)	P=0.008
Median (IQR) units of FFP transfused postoperatively	1 (0, 1)	1 (0, 1)	P=0.034
Median (IQR) units FFP transfused both intra- and postoperatively	1 (1, 1)	1 (1, 2)	P=0.001
Clinical importance 1		Clinical relevance 1	
Median (IQR) units of platelets transfused intraoperatively	0(0, 1)	1 (0, 1)	P=0.004
Median (IQR) units of platelets transfused postoperatively	1 (0, 1)	1 (0, 1)	P=0.028
Median (IQR) units of platelets transfused both intra- and postoperatively	1 (1, 1)	1 (1, 2)	P=0.001
1		1	
Median (IQR) allogeneic units transfused (PRBC, FFP, and platelets)	2 (1-3)	3 (2-4)	P=0.001
Clinical importance 1		1	
EXTERNAL VALIDITY			
Generalisability			

The study population were all undergoing surgery i.e. were the same as the target population. Two relevant groups were compared i.e. one undergoing POC testing and one undergoing clinician determined transfusion based on conventional lab tests. However, eligibility criteria prevented the inclusion of the full range of patients that may be expected in a normal practice.
Applicability
Reduced, study performed in Istanbul Turkey – study population characteristics and healthcare system likely to differ from that in Australia/New Zealand. This patient population was undergoing elective surgery for first time CABG with cardiopulmonary bypass and was without severe co-morbidities.
Comments
FU period was not clear and at 30 days there was no difference in early clinical outcome – late clinical outcomes not reported. The two groups were not completely matched for tests which may have favoured the TEG group. Summary Differentiation between surgical and non-surgical bleeding in patients with excessive MCTD was more successful in the TEG group and there were fewer transfusion units (FFP and platelets) required in the TEG group. There were no differences between the two groups in terms of consumption of red blood cells (packed cells), no of patients re-explored for bleeding, and early mortality.

Citation		
Avidan M.S., Alcock E.L. et al. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. British Journal of Anaesthesia. 2004; 2:176-86.		
Affiliation/Source of funds		
Department of Anesthesiology and Blood Bank, Washington University School of Medicine, St Louis, USA. Departments of Anaesthesia and Cardiothoracic Surgery, King's College Hospital, London, UK. Department of Haematology, Guy's, King's and St Thomas' Medical School (GKT), London, UK The Royal College of Anaesthetists (British Journal of Anaesthesia Small Project Grant, Oxford, UK) and the National Blood Services (London, UK) provided financial support for this research. Medicell UK provided thromboelastography consumables at discounted prices and lent the investigators a thromboelastography machine. Medtronic provided the consumables for the Hepcon machine for the purposes of the study. Additional funds were raised by the Academic Department of Anaesthesia, King's College London.		
Study design	Level of evidence	Location/setting
Patients were randomised into two groups (point of care vs laboratory test). Blood loss and transfusion was compared between these two groups and with a retrospective case-control group, in which management of bleeding had been according to the clinician's discretion.	II and III (depending on comparator)	UK
Intervention	Comparator	
Algorithm based on near-patient haemostatic testing (v. clinical algorithm). POC devices used include ACT+/Junior, Hepcon HMS Hemostasis Management System, PFA-100 platelet function analyser; and two dual-channel TEG coagulation analysers used in parallel. N=51	Randomised comparator: algorithm using routine laboratory haemostatic tests. N=51 Historical comparator: Adults who had undergone routine CABG surgery with the same clinical team over a four-month period preceding the interventional study. They had received blood components on the basis of individual clinician's discretion. N=108	
Population characteristics		
Adults undergoing elective, first-time CABG with CPB		
Length of follow-up	Outcomes measured	
24 hours	Transfusion (incidence), transfusion (volume), Blood loss, Haemoglobin concentration, platelet count	

INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is not clear whether allocation was concealed from those responsible for recruiting subjects.	The treatment arms had similar baseline characteristics	The study was not blinded	None detected	No patients were lost to follow-up.
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group (Control)	Statistical significance	
Patients transfused with PRBCs	POC: 34/51 (67%)	Laboratory: 35/51 (69%) Clinician discretion: 92/108 (85%)	Chi-square test: P=0.01	
Patients transfused with FFP	POC: 2/51 (4%)	Laboratory: 0/51 (0%) Clinician discretion: 16/108 (15%)	Chi-square test: P=0.003	
Patients transfused with platelets	POC: 2/51 (4%)	Laboratory: 1/51 (2%) Clinician discretion: 14/108 (13%)	Chi-square test: P=0.02	
Median (IQR) 24 hour postoperative blood loss, mL	POC: 755 (606, 975)	Laboratory: 850 (688, 1095) Clinician discretion: 810 (550, 1295)	NR	
Median (IQR) postoperative haemoglobin concentration, g/dL	POC: 9.3 (8.4, 10.3)	Laboratory: 9.3 (8.5, 9.7) Clinician discretion: Not available	NR	
Median (IQR) postoperative 24 hour haemoglobin, g/dL	POC: 10.1 (9, 10.9)	Laboratory: 9.9 (9, 10.8) Clinician discretion: 10.1 (9.6, 10.8)	NR	
Median (IQR) postoperative platelet count, $X10^9$/L	POC: 131 (110, 165)	Laboratory: 140 (111, 168) Clinician discretion: Not available	NR	
Median (IQR) postoperative 24 hour platelet count, $X10^9$/L	POC: 149 (123, 187)	Laboratory: 159 (135, 200) Clinician discretion: 144 (121, 174)	NR	
Total units of PRBCs transfused	POC: 99	Laboratory: 93 Clinician discretion: 285	NR	
Median (IQR) volume of PRBCs transfused, mL	POC: 500 (0, 678)	Laboratory: 495 (0, 612) Clinician discretion: 512 (286, 962)	Kruskal-Wallis ANOVA: P=0.03	

Total units of platelets transfused	POC: 3	Laboratory: 2 Clinician discretion: 14	NR
Total units of FFP transfused	POC: 6	Laboratory: 0 Clinician discretion: 65	NR
Reoperation for bleeding	POC: 1/51 (2%)	Laboratory: 1/51 (2%) Clinician discretion: 3/108 (3%)	POC vs. Laboratory RR (95% CI): 1.00 (0.06, 15.56); P=1.00 POC vs. clinician discretion RR (95% CI): 0.71 (0.08, 6.62); P=0.76
EXTERNAL VALIDITY			
Generalisability			
The study was conducted in adults undergoing CABG with CPB but it may be somewhat generalisable to other elective surgeries.			
Applicability			
The study was conducted in the UK, however it is likely to also be applicable to the Australian context.			
Comments			

Citation				
Royston D. and von Kier S. Reduced haemostatic factor transfusion using heparinise-modified thromboelastography during cardiopulmonary bypass. British Journal of Anaesthesia. 2001; 4:575-8.				
Affiliation/Source of funds				
Department of Anaesthesia and Critical Care, Royal Brompton and Harefield NHS Trust, Harefield Hospital, Harefield, Middlesex, UK				
Study design	Level of evidence	Location/setting		
RCT	II	UK		
Intervention	Comparator			
Heparinase-modified thromboelastogram guided intraoperative algorithm N=30	Clinical criteria and laboratory-based tests N=30			
Population characteristics				
Adults undergoing cardiac surgery. Ten per cent of the patients in each series had a heart transplantation and were taking aspirin and/or warfarin immediately before surgery. About 50% of the patients in each group had revascularisation and were also taking aspirin, and required multiple grafts with a bypass time estimated to be greater than 100 minutes. The remaining 40% of the patients were having the Ross procedure, multiple valve or valve and revascularisation surgery. No patients were having repeat operations and none received prophylactic aprotinin, epsilon aminocaproic or tranexamic acid.				
Length of follow-up	Outcomes measured			
12 hours	Transfusion (incidence), transfusion (volume), blood loss			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Allocation was concealed from those responsible for recruiting subjects	Patient details were not significantly different between groups but showed a wide distribution of values for age (21 to 83 years) and bypass time (48 to 167 minutes)	The study was not blinded	None detected	There was no loss to follow-up
Overall quality assessment (descriptive)				
Poor				
RESULTS				

Outcome	Intervention group	Comparator group (Control)	Statistical significance
Patients transfused with blood components	5/30 (17%)	10/30 (33%)	P<0.05
Volume of blood components transfused	Five units of FFP and one pool of platelets	16 units of FFP and nine platelet pools	P<0.05
Median (IQR) 12 hour chest tube loss, mL	470 (295, 820)	390 (240, 820)	NR

EXTERNAL VALIDITY
Generalisability
The study was conducted in adults undergoing cardiac surgery, but the results are likely to be generalisable to other elective surgeries
Applicability
The study was conducted in the UK, and is likely to be applicable to the Australian context.
Comments

<table>
<tr><td colspan="3">Citation</td></tr>
<tr><td colspan="3">Shore-Lesserson L., Manspeizer H.E. et al. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesthesia and analgesia. 1999; 88:312-9.</td></tr>
<tr><td colspan="3">Affiliation/Source of funds</td></tr>
<tr><td colspan="3">Departments of Anesthesiology and Cardiothoracic surgery, Mount Sinai Medical Center, New York, New York.</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location/setting</td></tr>
<tr><td>RCT</td><td>II</td><td>USA hospital</td></tr>
<tr><td colspan="2">Intervention</td><td>Comparator</td></tr>
<tr><td colspan="2">TEG-guided transfusion algorithm. Data from the celite-activated TEG was used to guide transfusion therapy 10 minutes after protamine completion. Transfusion therapy was prescribed in the presence of bleeding:
1. Additional protamine (50 mg) was given if the heparinise modified TED R time was less than one half of the non-heparinise R time.
2. If bleeding persisted, 6 U of platelets was transfused if platelet count <100,000/μL and TEG MA <45mm.
3. If bleeding persisted, 2 U of FFP was given if R time was > 20 mm.
4. If bleeding persisted, 10 U of cryoprecipitate was transfused if fibrinogen level <100 mg/dL.
5. If bleeding persisted and if the TEG showed evidence of fibrinolysis (LY30 > 7.5%), additional antifibrinolytic therapy (EACA 10g) was given at the discretion of the physicians caring for the patient. In both groups, if a patient received a transfusion, the abnormal tests were repeated and treated in accordance with the algorithm as long as the patient was still in the operating room.
(N=53)</td><td>Standard laboratory-based transfusion therapy (TEQ). Data from laboratory-based tests were used to guide transfusion therapy 10 minutes after protamine completion:
1. Additional protamine (50 mg) was given if ACT exceeded baseline by 15%.
2. If bleeding persisted, 6 U of platelets was transfused if platelet count <100,000/μL.
3. If bleeding persisted, 2 U of FFP was given if PT > 150% of control.
4. If bleeding persisted, 10 U of cryoprecipitate was transfused if fibrinogen level <100 mg/dL.
5. If bleeding persisted and if above therapy failed to reduce bleeding, an additional bolus of antifibrinolytic therapy (EACA 10g) was given at the discretion of the physicians caring for the patient.
(N=52)</td></tr>
<tr><td colspan="3">Population characteristics</td></tr>
<tr><td colspan="3">Adults undergoing a cardiac surgical procedure with a moderate to high risk for requiring a transfusion.</td></tr>
<tr><td colspan="2">Length of follow-up</td><td>Outcomes measured</td></tr>
<tr><td colspan="2">Two days postoperative</td><td>Mortality, reoperation for bleeding, Morbidity, clotting time, platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen concentration, transfusion (incidence), transfusion (volume)</td></tr>
</table>

INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomisation achieved via a table of random numbers. It is unclear whether allocation was blinded from those responsible for recruiting subjects.	The baseline characteristics were similar between treatment arms.	The anaesthesiologist and surgeon caring for the patient were blinded to the patient's group assignment. All intraoperative results of the TEG and laboratory coagulation tests were interpreted by an anaesthesiologist investigator not directly involved with the patient's care. The recommended therapy according to the patient's group assignment was communicated to the anaesthesiologist and surgeon by this investigator as appropriate.	None detected	Two patients in the TEG group were not included in follow-up analyses. One patient enrolled but not studied was undergoing cardiac reoperation and was placed emergently on CPB because of massive hemorrhage during sternotomy. The patient was excluded from the study at theis time. The other patient who did not complete the protocol was excluded due to a severe protamine reaction that required immediate reinstitution of CPB.
Overall quality assessment (descriptive)				
Fair				

RESULTS			
Outcome	Intervention group	Comparator group (Control)	Statistical significance
Mortality (ITT)	0/53 (0%)	2/52 (4%)[1]	RevMan: RR (95% CI): 0.20 (0.01, 3.99); P=0.29
Reoperation for bleeding (ITT)	0/53 (0%)	2/52 (4%)[2]	RevMan: RR (95% CI): 0.20 (0.01, 3.99); P=0.29
Cerebrovascular ischemic event (ITT)	1/53 (2%)	0/52 (0%)	RevMan: RR (95% CI): 2.94 (0.12, 70.67) P=0.51
Mean (SD) activated clotting time[3] (baseline), seconds	165 (34)	170 (49)	Instat: Mean difference (95% CI): 5.0 (-11.5, 21.5); P=0.55
Mean (SD) activated clotting time[3] (post-protamine), seconds	158 (93)	149 (20)	Instat: Mean difference (95% CI): -9.0 (-35.2, 17.2); P=0.50
Mean (SD) platelet count[4] (baseline), X1000/μL	203 (66)	200 (78)	Instat: Mean difference (95% CI): -3.0 (-31.3, 25.3); P=0.83

Mean (SD) platelet count[4] (warming on CPB), X1000/μL	92 (79)	96 (79)	Instat: Mean difference (95% CI): 4.0 (-26.9, 34.9); P=0.80
Mean (SD) platelet count[4] (ICU), X1000/μL	111 (48)	120 (48)	Instat: Mean difference (95% CI): 9 (-9.8, 27.8); P=0.34
Mean (SD) prothrombin time[5] (baseline), seconds	13.0 (1.1)	12.9 (1.3)	Instat: Mean difference (95% CI): -0.1 (-0.6, 0.4); P=0.67
Mean (SD) prothrombin time[5] (post-protamine), seconds	18.1 (2.3)	21.3 (26)	Instat: Mean difference (95% CI): 3.2 (-4.1, 10.5); P=0.38
Mean (SD) prothrombin time[5] (ICU), seconds	16.1 (1.7)	15.7 (1.6)	Instat: Mean difference (95% CI): -0.4 (-1.0, 0.2); P=0.22
Mean (SD) activated partial thromboplastin time[6] (baseline), seconds	31.6 (6.9)	34.1 (13.1)	Instat: Mean difference (95% CI): 2.5 (-1.6, 6.6); P=0.23
Mean (SD) activated partial thromboplastin time[6] (post-protamine), seconds	52.2 (48.0)	43.0 (14)	Instat: Mean difference (95% CI): -9.2 (-23.0, 4.6); P=0.19
Mean (SD) activated partial thromboplastin time[6] (ICU), seconds	35.9 (6.1)	36.8 (10.2)	Instat: Mean difference (95% CI): 0.9 (-2.4, 4.2); P=0.59
Mean (SD) fibrinogen concentration[7] (baseline), mg/dL	409 (82)	416 (118)	Instat: Mean difference (95% CI): 7 (-32.8, 46.8); P=0.73
Mean (SD) fibrinogen concentration[7] (post-protamine), mg/dL	239 (86)	246 (86)	Instat: Mean difference (95% CI): 7.0 (-26.6, 40.6); P=0.68
Mean (SD) fibrinogen concentration[7] (ICU), mg/dL	259 (95)	263 (118)	Instat: Mean difference (95% CI): 4.0 (-37.9, 45.9); P=0.85
Patients transfused with allogeneic blood components (total)	22/53 (42%)	34/52 (65%)	P=0.01
Patients transfused with packed red blood cells (intraoperative)	17/53 (32%)	23/52 (44%)	P=0.2
Patients transfused with packed red blood cells (postoperative)	10/53 (19%)	16/52 (31%)	P=0.16
Patients transfused with packed red blood cells (total)	22/53 (42%)	31/52 (60%)	P=0.06
Patients transfused with FFP (intraoperative)	3/53 (6%)	8/52 (15%)	P=0.1
Patients transfused with FFP (postoperative)	2/53 (4%)	11/52 (21%)	P<0.007
Patients transfused with FFP (total)	4/53 (8%)	16/52 (31%)	P=0.002

Patients transfused with platelet concentrates (intraoperative)	5/53 (9%)	8/52 (15%)	P=0.4
Patients transfused with platelet concentrates (postoperative)	3/53 (6%)	9/52 (17%)	P=0.06
Patients transfused with platelet concentrates (total)	7/53 (13%)	15/52 (29%)	P<0.05
Mean (SD) volume of PRBCs transfused (intraoperative), mL	267 (423)	346 (449)	P=0.4
Mean (SD) volume of PRBCs transfused (postoperative), mL	103 (252)	177 (318)	P=0.27
Mean (SD) volume of PRBCs transfused (total), mL	354 (487)	475 (593)	P=0.12
Mean (SD) volume of FFP transfused (intraoperative), mL	22 (101)	113 (407)	P=0.4
Mean (SD) volume of FFP transfused (postoperative), mL	33 (169)	146 (378)	P=0.13
Mean (SD) volume of FFP transfused (total), mL	36 (142)	217 (463)	P<0.04
Mean (SD) volume of platelet concentrates transfused (intraoperative), mL	22 (75)	41 (122)	P=0.6
Mean (SD) volume of platelet concentrates transfused (postoperative), mL	11 (46)	42 (107)	P=0.3
Mean (SD) volume of platelet concentrates transfused (total), mL	34 (94)	83 (160)	P=0.16
Mean (SD) six-hour mediastinal drainage, mL	362 (274)	469 (637)	P=0.63
Mean (SD) 24-hour mediastinal drainage, mL	702 (500)	901 (847)	P=0.27
EXTERNAL VALIDITY			
Generalisability			
The study is in patients undergoing cardiac surgery, but the results are somewhat generalisable to other surgery types.			
Applicability			
The study was conducted in New York, and although there are differences in health care systems, the results are likely to be applicable to the Australian context.			
Comments			

[1] Both patients died from hemodynamic causes in the postoperative period.
[2] In one patient, a specific surgical source of bleeding was discovered.
[3] Normal range: 90 to 120 seconds
[4] Normal range: 120 to 500 X1000/μL
[5] Normal range: 12 to 14 seconds
[6] Normal range: 25 to 34 seconds
[7] Normal range: 150 to 500 mg/dL

<table>
<tr><td colspan="4">Citation</td></tr>
<tr><td colspan="4">Westbrook AJ., Olsen J. et al. Protocol based on thrombolestaograph (TEG) out-performs physician preference using laboratory coagulation tests to guide blood replacement during and after cardiac surgery: a pilot study. Heart , Lung and Circulation.2009;18:277-288.</td></tr>
<tr><td colspan="4">Affiliation/Source of funds</td></tr>
<tr><td colspan="4">Department of Intensive Care and Hyperbaric Medicine, Alfred Hospital, Melbourne, Australia.
Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia.
Department of Surgery, Monash University, Melbourne Australia.
Funding for the salary of the research nurse was provided by Ventracor PTY LTD, and Medtel PTY LTD, Australia.</td></tr>
<tr><td>Study design</td><td colspan="2">Level of evidence</td><td>Location/setting</td></tr>
<tr><td>RCT
Randomisation method not reported</td><td colspan="2">II</td><td>Australia, Hospital</td></tr>
<tr><td colspan="2">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="2">TEG (N=32)
Time taken before clot formation begins
Time taken for clot to form
Maximum strength of the clot
Clot strength maintenance and clot lysis

A strict protocol for administration of blood products was used based on a computerised thromboelastograph coagulation analyser (Haemoscope Corp., Skokie, IL)</td><td colspan="2">Physician directed product administration (control) (N=37)
With reference to laboratory coagulation tests
• APTT
• INR
• Fibrinogen and platelet count
and physician's previous experience.</td></tr>
<tr><td colspan="4">Population characteristics</td></tr>
<tr><td colspan="4">All patients presenting for cardiac surgery with the exception of lung transplantation were included (N=69)
Heparin for cardiopulmonary bypass was administered according to standard activated clotting time in both groups</td></tr>
<tr><td colspan="2">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="2">Not reported but at least until discharge (7-13 days)</td><td colspan="2">Re-sternotomy,
Minimum haemoglobin,
Ttransfusion of RBC,PLTS,FFP,CRYO
Intubation time
ICU stay</td></tr>
</table>

INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomisation (method not reported)	Both groups were satisfactorily matched (i.e. ns differences) by most measured characteristics including age (mean ages for control and TEG = 61 and 66 years) and gender (28% and 31%), preoperative aspirin (24% and 24%),heparin (5% and 9%), warfarin (10% and 16 %) and clopidogrel (3% and 6%). Exceptions were the % of "redo" surgery which was mostly confined to the TEG group (p = 0.04) and bicarbonate levels post bypass which were higher in the TEG group (p = 0.04)	Surgeons were blinded to the method of haemostasis. It is not stated who made the decision to transfuse/assess other outcomes and if they were blinded to the patient's group allocation, however appended protocol flow diagrams for the various protocols used suggest that the decision to transfuse was not blinded to intervention group.	A potential confounder in the TEG group was reported to be the "Hawthorn effect"[7] which may have exaggerated the trend towards a better outcome in this group.	All patients included in the analysis.
Overall quality assessment (descriptive)				
Fair				

RESULTS			
Outcome	Intervention group TEG N=32	Comparator group (Control) Physician directed product administration with reference to APTT, INR, fibrinogen and platelet count N=37	Statistical significance
Units of blood products transfused intraoperatively	19	44	ns (p value not reported)
Units of blood products transfused in ICU	18	46	ns (p value not reported)
Total units of blood products transfused	37	90	ns (p value not reported)

[7] A term referring to the tendency of some people to work harder and perform better when they are participants in an experiment.

Clinical importance 4		Clinical relevance 1	
Units of PRBCs transfused intraoperatively	11	15	ns (p value not reported)
Units of PRBCs transfused in ICU	3	18	ns (p value not reported)
Total units of PRBCs transfused	14	33	ns (p value not reported)
Clinical importance 2		Clinical relevance 1	
Units of FFP transfused intraoperatively	8	14	ns (p value not reported)
Units of FFP transfused postoperatively	10	8	ns (p value not reported)
Total units of FFP transfused	18	22	ns (p value not reported)
Clinical importance 2		Clinical relevance 1	
Units of platelets transfused intraoperatively	0	10	ns (p value not reported)
Units of platelets transfused postoperatively	5	5	ns (p value not reported)
Total units of platelets transfused	5	15	ns (p value not reported)
Clinical importance 2		Clinical relevance 1	
Units of cryoprecipitate transfused intraoperatively	0	5	ns(p value not reported)
Units of cryoprecipitate transfused postoperatively	0	15	ns(p value not reported)
Total units of cryoprecipitate transfused	0	20	ns(p value not reported)
Clinical importance 2		Clinical relevance 1	
Median Blood loss in mls (25th & 75th percentile)	875 (755-1130)	960 (820-1200)	ns (p = 0.437)
Clinical importance 2		Clinical relevance 1	
Median intubation time in hours 25th & 75th percentile)	8 (5.3-19.8)	10.3 (5.8-19.5)	ns (p value not reported)
Clinical importance 2		Clinical relevance 1	
Median minimum (IQR) haemoglobin concentration, g/l	87 (83-94)	86 (82-104)	ns (p value not reported)

Clinical importance 3		Clinical relevance 1	
Median (IQR) length of ICU stay, hours	29.4 (14.3, 56.4)	32.5 (22, 74.5)	ns (p value not reported)
Median (IQR) length of hospital stay, days	9 (7-13) *Extra day not due to bleeding	8 (7-12)	ns (p value not reported)
Clinical importance 3		Clinical relevance 3	
EXTERNAL VALIDITY			
Generalisability			
Good- surgical population similar to target guideline population, POC compared to a relevant/appropriate control.			
Applicability			
High- the study reports a cohort of patients undergoing cardiac surgery in a large Australian hospital.			
Comments			
The authors point to an 'impressive reduction (52% per patient) in blood products administered peri operatively' and a 'clinically significant reduction in the administration of blood products'. Small group size and non-parametric testing and a high proportion of redo study patients (18.7%) in the TEG group were reported as possible reasons for the failure of the differences between the two study groups to reach significance. However, all outcome parameters (with the exception of the hospital LOS) were consistently more favourable for the TEG group. This was a pilot study – a larger RCT was planned but slow recruitment to the pilot study and lack of funds precluded a larger RCT (personal communication from Professor Bob Salamonsen 12th March 2010.[8] Note: ICU results not included.			

[8] 'After the pilot trial for the TEG (westbrook et al.) we did not perform or plan a followup trial. We were troubled by a very low recruitment rate and obtained only the patients reported in the paper during a whole year - hence our decision to call it a pilot trial. After one year the money dried up'.

Level III evidence

Citation		
Spalding, GJ., Hartrumpf, M. et al. Cost reduction of peri operative coagulation management in cardiac surgery: value of "bedside" thrombelastography (ROTEM). European Journal of Cardiothoracic Surgery 2007;31:1052-1057.		
Affiliation/Source of funds		
Department of Cardiovascular Surgery, Heart Center Brandenburg, Bernau/Berlin. Department of Anaesthesiology, Heart Center Brandenburg, Bernau/Berlin. Conflict of interest/ source of funds =None declared		
Study design	Level of evidence	Location/setting
Before and after cohort design, single institution	III-3	Germany, Hospital,

Intervention	Comparator
ROTEM [9](bedside instrument measuring clot formation and dissolution indicating changes in coagulation, platelet function, platelet-fibrinogen interaction and fibrinolysis). N=693	No ROTEM N=729
Population characteristics	
All patients in a single institution undergoing cardiosurgical therapy over a 12 month period. Age 67 years ± 8-9years, males 70.6%-74.5%.	
Length of follow-up	Outcomes measured
1 year	Blood consumption Blood product consumption Coagulation product consumption Cumulative costs Operative risk/early mortality Early Resternotomy

INTERNAL VALIDITY

Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Within a 1 year period (exact dates not given) Patients undergoing surgery in the first six months were assigned to the No ROTEM control group. Patients	The cohort did not all receive the same surgical procedure. 71% of the comparator and 72% of the ROTEM group had isolated coronary artery revascularization (CABG) 3.3% of the comparator and 1.9% of the ROTEM group had CABG without cardiopulmonary bypass	Not reported	Cannot be ruled out - time periods were different.	All study patients were reported no losses to follow up.

[9] ROTEM® stands for rotation thromboelastometry and is an enhancement of classical thromboelastography, which is a technique for the assessment of blood coagulation disorders.

undergoing surgery in the second six months were assigned to the ROTEM intervention group.	15% of the comparator and 12% of the ROTEM group had isolated valve surgery 9.5% of the comparator and 10.6% of the ROTEM group had CABG + valve surgery 2.9% of the comparator and 3.5% of the ROTEM group had aortic surgery 1.4% of the comparator and 1.6% of the ROTEM group had other measures Demographic data between the two groups did not differ statistically in terms of age (mean age =67yrs), gender (71-74% male) surgery type, early mortality and early resternotomy for bleeding. The ROTEM group had a significantly higher EuroSCORE[10] (p=0.006).			

Overall quality assessment (descriptive)			
Fair			
RESULTS			
Outcome	Intervention group ROTEM (second six month period)	Comparator group No ROTEM (first six month period)	Statistical significance
Red blood cell unit (€ 70.00)	368	439	ns
Clinical importance 3		Clinical relevance 1	
Platelet concentrate unit (€ 500.0)	28	59	p = 0.000
Clinical importance 1		Clinical relevance 1	
Fresh frozen plasma unit (€ 51.00)	116	118	ns
Clinical importance 3		Clinical relevance 1	

[10] Euro SCORE is a method of calculating predicted operative mortality for patients undergoing cardiac surgery.

Pooled coagulation concentrates - 500 units (€120)	27	130	p = 0.000
Clinical importance 1		Clinical relevance 1	
Fibrinogen (1 g, €287.50)	55	14	ns (0.060)
Clinical importance 3		Clinical relevance 1	
rFactor VIIa (120 IU, € 1512.00)	1	11	p= 0.000
Clinical importance 1		Clinical relevance 1	
Factor XIII (1250 IU,€ 405.00)	8	17	p = 0.001
Cumulative monthly costs total Cumulative monthly costs blood products Cumulative monthly costs coagulation factor	€55,925 €45,000 €30,000	€125,828 €66.000 €60,000	-44% -32% -50%
Clinical importance Not reported		Clinical relevance Not relevant	
Mean EuroSCORE (SD) (European System for Cardiac Operative Risk Evaluation)	5.5 ± 3.1	5.0 ±3.3	p=0.006
Clinical importance 1		Clinical relevance 3	
Early resternotomy (%)	5.5	6.6	ns (0.384)
Clinical importance 3		Clinical relevance 1	
Early mortality (%)	6.0	5.9	ns
Clinical importance 3		Clinical relevance 1	
EXTERNAL VALIDITY			
Generalisability			
The patient population were undergoing cardiac surgery i.e. they were part of the guideline target population, a POC system was the focus of the cost assessment and the comparator was normal clinical practice prior to the implementation of the ROTEM system.			
Applicability			
In general the results have reasonable applicability to any large specialist hospital carrying out this type of surgery. However, the cost analysis was representative only of the health system in which the study was carried out and may not pertain to other countries or health systems. Moreover, a full cost-effectiveness analysis was not carried out.			
Comments			
ROTEM was performed with a blood loss of over 200ml/h which did not cease after 2 hr. ROTEM was not performed in the majority of patients (65%) who presented with a regular postoperative drainage loss. The study is subject to the limitations of pre-post/before-after studies. Cost analysis was very rudimentary- only direct cost reductions were considered.			

Intervention 8 – Administration of antifibrinolytics & DDAVP

Level I evidence

STUDY DETAILS				
Citation				
A Abrishami, F Chung, J Wong (2009) Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. Can J Anesth 56: 202-212.				
Affiliation/Source of funds				
Department of Anesthesia, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada. Funding: Department of Anesthesia, Toronto Western Hospital, University Health Network				
Study design	Level of evidence	Location/setting		
Systematic review including 8 RCTs that investigated the effects of topical application of antifibrinolytic drugs on blood loss and transfusion requirements in patients undergoing on-pump cardiac bypass surgery.	Level I	Hospital		
Intervention	Comparator			
Topical application of aprotinin or tranexamic acid. Poured into pericardial cavity and/or over mediastinal tissues at the end of surgery or and before closure of the median sternotomy	Placebo or active			
Population characteristics				
Patients undergoing on-pump cardiac surgery (primary operation only)				
Length of follow-up	Outcomes measured			
Not specified	24-hour chest tube blood loss, units of allogenic RBC transfusion, incidence of allogenic RBC transfusion			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all eight studies. Method of randomisation reported in five studies.	Baseline characteristics of intervention and control groups not reported. Methodological quality of studies assessed independently by two authors. Disagreements resolved by a third author. Data extraction for each study not stated. A random effects model was use in the meta-analyses as all showed statistical heterogeneity.	Five studies were double blinded. One study was not blinded. The blinding status of two studies was unclear.	Egger's test for bias was non-significant (p=0.6 and p=0.5) for reduction of blood loss or amount of blood transfusion, suggesting that there was no publication bias.	States all 8 studies had "adequate" follow-up
Overall quality assessment (descriptive)				
Good. This review clearly defined the research question, scope, search terms and inclusion/exclusion criteria. The search strategy employed appeared robust, and the methods for analysis were appropriate. The summary, as well as a quality rating, for each included study was provided. This review provided pooled data, for each of the specified outcomes, through meta-analysis of the data from included studies.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Topical aprotinin vs placebo				
24-hr postoperative chest tube blood loss 5 trials (N=324)	NR	NR	WMD -204 ml (95%CI : -276, -132) P<0.001 (P*het*=0.04)	
Allogenic RBC transfusion (units) 4 trials (N=229)	NR	NR	WMD -0.83 (95%CI : -1.21, -0.44) P=<0.001 (P*het*=0.34)	

Allogenic RBC transfusion (incidence) 3 trials (N=341)	97/179 (13.5)	108/162 (66.7)	RR 0.72 (95%CI : 0.47, 1.08) P=0.11 (P*het*=0.008)
Topical tranexamic acid vs placebo			
24-hr postoperative chest tube blood loss 4 trials (N=269)	NR	NR	WMD -250 ml (95%CI : -465, -35) P=0.02 (P*het*<0.001)
Allogenic RBC transfusion (units) 3 trials (N=229)	NR	NR	WMD -1.58 (95%CI : -2.26, -0.90) P=<0.001 (P*het=0.29)*
Allogenic RBC transfusion (incidence) 2 trials (N=233)	54/117 (46.2)	55/116 (47.4)	RR 0.98 (95%CI : 0.75, 1.27) P=0.88 (P*het=0.69)*

Outcome	Clinical importance	Clinical relevance
Topical aprotinin vs placebo		
24-hr postoperative chest tube blood loss	1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Allogenic RBC transfusion (units)	1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Allogenic RBC transfusion (incidence)	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Topical tranexamic acid vs placebo		
24-hr postoperative chest tube blood loss	1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Allogenic RBC transfusion (units)	1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Allogenic RBC transfusion (incidence)	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.

EXTERNAL VALIDITY
Generalisability
This systematic review focuses on patients undergoing on-pump cardiac surgery, who may not share clinical characteristics with the general surgical patient population.
Applicability
The studies in this review were mostly conducted in developed countries (Croatia, Czech Republic, Egypt, England, Germany, Italy, Turkey), comparable to Australia. The surgeries performed (and the possible benefits) are likely to be relevant in the Australian context.
Comments
This review suggests that topical aprotinin and tranexamic acid may decrease blood loss and transfusion requirements.

Abbreviations: CI, confidence interval; *het*, heterogeneity; ITT, intention-to-treat; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

STUDY DETAILS				
Citation				
JR Brown, NJO Birkmeyer, GT O'Connor (2007) Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation 115: 2801-2813.				
Affiliation/Source of funds				
Center for the Evaluative Clinical Sciences and Departments of Medicine and of Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA; Michigan Surgical Collaboration for Outcomes Research and Evaluation, University of Michigan, Ann Arbor, Michigan, USA. Funding: Not stated.				
Study design	Level of evidence	Location/setting		
Systematic review including 138 RCTs that investigated the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery.	Level I	Hospital		
Intervention	Comparator			
Aprotinin, tranexamic acid, ε-aminocaproic acid	Placebo or active			
Population characteristics				
Adults undergoing CABG, isolated valve or combined CABG/valve surgery.				
Length of follow-up	Outcomes measured			
Not specified	Bleeding; incidence of transfusion; incidence or re-operation; adverse events (including mortality, stroke, MI); renal complications; renal dysfunction.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all 138 studies. Method of randomisation not reported in SR.	Baseline characteristics of intervention and control groups not reported. Data extraction conducted by two independent reviewers. Quality assessment conducted using Jadad score and determined not to influence results. A random effects model was use in the meta-analyses.	The majority of included studies were double-blinded.	Funnel plots generated to assess publication bias. Evidence of bias for aprotinin for total blood loss and incidence transfusion with pRBCs. Evidence of bias for aminocaproic acid and tranexamic acid for incidence of transfusion with pRBCs.	36/138 trials excluded patients from the analysis following randomis-ation
Overall quality assessment (descriptive)				
Fair. The search strategy employed was inadequate as it included Medline only. The methods for analysis were appropriate. The summary, as well as a quality rating, for each included study was provided, but no individual study results were provided. This review provided pooled data only, for each of the specified outcomes, through meta-analysis of the data from included studies. A number of data extraction errors were identified when examining one of the subgroup analyses.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)	
Aprotinin high dose vs placebo				
	Mean ± SD	Mean ± SD		
Total blood loss (mL) 22 trials (N=1760)	NR	NR	*High dose* WMD -348 (-416, -281) P<0.001 (P*het*=NR)	
	n/N (%)	n/N (%)		

Incidence of transfusion with pRBC 49 trials (N=4379)	NR	NR	*High dose* RR 0.60 (0.53, 0.67) P<0.001 (P*het*=NR)
Return to operating room 40 trials (N=3912)	NR	NR	*High dose* RR 0.47 (0.32, 0.69) P<0.001 (P*het*=NR)
Mortality 43 trials (N=6175)	NR	NR	*High dose* RR 0.89 (0.65, 1.21) P=0.46 ((P*het*=NR)
Stroke 22 trials (N=1737)	NR	NR	*High dose* RR 0.67 (0.30, 1.47) P=0.32 (P*het*=NR)
Myocardial infarction 31 trials (N=3315)	NR	NR	*High dose* RR 1.10 (0.83, 1.45) P=0.52 (P*het*=NR)
Renal failure 27 trials (N=4681)	NR	NR	*High dose* RR 1.09 (0.68, 1.77) P=0.71 (P*het*=NR)
Renal dysfunction 19 trials (N=1778)	NR	NR	RR 1.47 (1.12, 1.94) P=0.006 (P*het*=NR)
Aprotinin low dose vs placebo			
	Mean ± SD	Mean ± SD	
Total blood loss (mL) 6 trials (N=515)	NR	NR	WMD -226 (-277, -175) P<0.001 (P*het*=NR)
	n/N (%)	n/N (%)	
Incidence of transfusion with pRBC 20 trials (N=1645)	NR	NR	RR 0.76 (0.66, 0.86) P<0.001 (P*het*=NR)
Return to operating room 20 trials (N=1623)	NR	NR	RR 0.69 (0.41, 1.18) P=0.18 (P*het*=NR)
Mortality 14 trials (N=1453)	NR	NR	RR 1.37 (0.72, 2.59) P=0.34 (P*het*=NR)
Stroke 10 trials (N=1049)	NR	NR	RR 0.47 (0.09, 2.36) P=0.36 (P*het*=NR)
Myocardial infarction 16 trials (N=1585)	NR	NR	RR 0.94 (0.58, 1.54) P=0.82 (P*het*=NR)
Renal failure 7 trials (N=786)	NR	NR	RR 1.86 (0.07, 49.3) P=0.71 (P*het*=NR)
Renal dysfunction 9 trials (N=1041)	NR	NR	RR 1.01 (0.69, 1.49) P=0.96 (P*het*=NR)
E-amino caproic acid vs placebo			
	Mean ± SD	Mean ± SD	
Total blood loss (mL) 3 trials (N=144)	NR	NR	WMD -240 (-341, -140) P<0.001 (P*het*=NR)
	n/N (%)	n/N (%)	
Incidence of transfusion with pRBC 10 trials (N=628)	NR	NR	RR 0.63 (0.44, 0.90) P=0.01 (P*het*=NR)
Return to operating room 9 trials (N=851)	NR	NR	RR 0.51 (0.15, 1.82) P=0.30 (P*het*=NR)
Mortality 6 trials (N=735)	NR	NR	RR 1.82 (0.55, 5.98) P=0.32 ((P*het*=NR)
Stroke 8 trials (N=833)	NR	NR	RR 0.60 (0.13, 2.81) P=0.52 (P*het*=NR)
Myocardial infarction 8 trials (N=839)	NR	NR	RR 1.14 (0.50, 2.60) P=0.76 (P*het*=NR)

Renal failure 0 trials	-	-	-
Renal dysfunction 0 trials	-	-	-
Tranexamic acid vs placebo			
	Mean ± SD	Mean ± SD	
Total blood loss (mL) 11 trials (N=1100)	NR	NR	WMD -285 (-394, -175) P<0.001 (P*het*=NR)
	n/N (%)	n/N (%)	
Incidence of transfusion with pRBC 22 trials (N=2429)	NR	NR	RR 0.75 (0.60, 0.92) P=0.007 (P*het*=NR)
Return to operating room 21 trials (N=2255)	NR	NR	RR 0.70 (0.44, 1.11) P=0.13 (P*het*=NR)
Mortality 18 trials (N=2229)	NR	NR	RR 0.67 (0.33, 1.37) P=0.28 ((P*het*=NR)
Stroke 15 trials (N=2098)	NR	NR	RR 1.31 (0.59, 2.93) P=0.51 (P*het*=NR)
Myocardial infarction 16 trials (N=2219)	NR	NR	RR 0.94 (0.51, 1.74) P=0.85 (P*het*=NR)
Renal failure 3 trials (N=840)	NR	NR	RR 1.43 (0.30, 6.85) P=0.66 (P*het*=NR)
Renal dysfunction 4 trials (N=684)	NR	NR	RR 2.02 (0.73, 5.60) P=0.18 (P*het*=NR)

Outcome	Clinical importance	Clinical relevance
Aprotinin high dose vs placebo/no treatment		
Total blood loss	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Incidence of transfusion with pRBC	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Return to operating room	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Mortality	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Stroke	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Renal failure	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Renal dysfunction	1: Clinically important *harm*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Aprotinin low dose vs placebo/no treatment		
Total blood loss	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Incidence of transfusion with pRBC	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.

Return to operating room	2: Point estimate shows clinically important *benefit*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Mortality	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Stroke	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Renal failure	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Renal dysfunction	4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
E-aminocaproic acid vs placebo/no treatment		
Total blood loss	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Incidence of transfusion with pRBC	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Return to operating room	2: Point estimate shows clinically important *benefit*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Mortality	2: Point estimate shows clinically important *harm* but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Stroke	2: Point estimate shows clinically important *benefit*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Myocardial infarction	2: Point estimate shows clinically important *harm*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Renal failure	NA	1: Patient-relevant clinical outcome.
Renal dysfunction	NA	1: Patient-relevant clinical outcome.
Tranexamic acid vs placebo/no treatment		
Total blood loss	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Incidence of transfusion with pRBC	1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Return to operating room	2: Point estimate shows clinically important *benefit*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Mortality	2: Point estimate shows clinically important *benefit* but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Stroke	2: Point estimate shows clinically important *harm*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.

Myocardial infarction	2: Point estimate shows clinically important *benefit*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Renal failure	2: Point estimate shows clinically important *harm*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
Renal dysfunction	2: Point estimate shows clinically important *harm*, but confidence limit includes null value.	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on adults undergoing cardiac surgery (CABG, valve or CABG+valve), who are unlikely to share clinical characteristics with the general surgical patient population.		
Applicability		
The location of the included studies in this review was not stated, however it includes a large number of studies so likely to be largely applicable. The surgeries performed (and the possible benefits) are likely to be relevant in the Australian context.		
Comments		

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; *het*, heterogeneity; ITT, intention to treat; MI, myocardial infarction; NA, not applicable; NR, not reported; pRBC, packed red blood cells; RCT, randomised controlled trial; RR, risk ration; SR, systematic review; WMD, weighted mean difference.

[a] Includes one trial in which aprotinin + ε-aminocaproic acid was compared with ε-aminocaproic acid only.

[b] Discrepancy between Figure 2 and text. Data taken from Figure 2.

STUDY DETAILS				
Citation				
PA Carless, BJ Stokes, AJ Moxey, DA Henry (2004) Desmopressin use for minimising perioperative allogenic blood transfusion. Cochrane Database of Systematic Reviews. Issue 1. Article No.: CD001884. DOI: 10.1002/14651858.CD001884.pub2.				
Affiliation/Source of funds				
Discipline of Clinical Pharmacology, Faculty of Health, University of Newcastle, Newcastle, Australia; Institute of Clinical Evaluative Sciences, Toronto, Canada. Funding: Special purpose grant, Hunter Area Pathology Services, NSW, Australia; Australian Health Ministers' Advisory Committee, NHMRC, Australia.				
Study design	Level of evidence		Location/setting	
Systematic review including 29 RCTs that investigated the effectiveness and adverse outcomes of desmopressin use in reducing perioperative blood loss.	Level I		Hospital	
Intervention		Comparator		
Desmopressin acetate administered intravenously as prophylactic therapy during the perioperative period. Variable doing regimens were used in the included trials.		Placebo		
Population characteristics				
Adults undergoing surgery who did not have congenital bleeding disorders.				
Length of follow-up		Outcomes measured		
Not specified		Incidence of transfusion; volume of transfusion; blood loss; re-operation due to bleeding; mortality; myocardial infarction; stroke; thrombosis		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all 29 studies. Method of randomisation inadequate or not reported in 22 trials.	Baseline characteristics of intervention and control groups not reported. Study inclusion and quality assessment conducted by two independent reviewers. Quality assessment conducted using criteria proposed by Schulz. Number of reviewers carrying out data extraction not stated. Meta-analysis performed using Review Manager using a random effects model.	26/29 trials double-blind; 2/29 unclear, and 1/29 not double-blind	Funnel plots generated to assess publication bias. Little evidence of publication bias for incidence of blood transfusion and blood loss. Appears to be no measurement or treatment bias.	11/29 trials reported no exclusions or ITT analysis; 17/29 reported exclusions but these judged unlikely to cause bias; 1/29 exclusions not reported.
Overall quality assessment (descriptive)				
Good. The search strategy employed was adequate and the methods for analysis were appropriate. The summary, as well as a quality rating, for each included study was provided. This review provided pooled data, for each of the specified outcomes, through meta-analysis of the data from included studies. The authors note that the methodological quality of most of the included studies was poor				
RESULTS				

Outcome No. trials (N) *No. trials included in analysis (N)*[a]	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)
Desmopressin vs placebo			
	n/N (%)	n/N (%)	
Incidence of transfusion 19 trials (N=1387) *17 trials (N=1308)*	383/703 (54.5)	377/684 (55.1)	*All studies* RR 0.96 (0.87, 1.06) P=0.42 (P*het*=0.19)
Incidence of transfusion 15 trials (N=1196) *14 trials (1137)*	341/610 (55.9)	330/586 (56.3)	*Cardiac surgery* RR 0.95 (0.84, 1.07) P=0.39 (P*het*=0.11)
Incidence of transfusion 4 trials (N=191) *3 trials (N=171)*	42/93 (45.2)	47/98 (48.0)	*Miscellaneous surgery* RR 1.01 (0.81, 1.26) P=0.91 (P*het*=0.59)
Incidence of transfusion 9 trials (N=586) *8 trials (N=527)*	150/299 (50.2)	158/287 (55.1)	*Cardiac surgery/Primary CABG* RR 0.85 (0.73, 0.99) P=0.038 (P*het*=0.43)
Incidence of transfusion 6 trials (N=610)	191/311 (61.4)	172/299 (57.5)	*Cardiac surgery/CABG + valve ± combination/redo surgery* RR 1.03 (0.88, 1.19) P=0.75 (P*het*=0.14)
Incidence of transfusion 6 trials (N=399) *5 trials (N=340)*	91/192 (47.4)	103/207 (49.8)	*Cardiac surgery/ASA use* RR 0.89 (0.64, 1.23) P=0.49 (P*het*=0.12)
Incidence of transfusion 4 trials (N=286)	69/153 (45.1)	73/133 (54.9)	*Cardiac surgery/no ASA use* RR 0.79 (0.62, 1.01) P=0.056 (P*het*=0.36)
Incidence of transfusion 10 trials (N=736)	180/373 (48.3)	190/363 (52.3)	*Transfusion protocol* RR 0.90 (0.77, 1.04) P=0.16 (P*het*=0.25)
Incidence of transfusion 9 trials (N=651) *7 trials (N=572)*	203/330 (61.5)	187/321 (58.3)	*No transfusion protocol* RR 1.03 (0.93, 1.14) P=0.60 (P*het*=0.40)
Incidence of transfusion 10 trials (N=732) *9 trials (N=673)*	242/382 (63.4)	237/350 (67.7)	*No autologous techniques used* RR 0.91 (0.78, 1.07) P=0.25 (P*het*=0.04)
Incidence of transfusion 9 trials (N=655) *8 trials (N=635)*	141/321 (43.6)	140/334 (41.9)	*Autologous techniques used* RR 1.00 (0.84, 1.19) P=0.97 (P*het*=0.31)
Incidence of transfusion 3 trials (N=249) *2 trials (N=190)*	73/124 (58.9)	74/125 (59.2)	*Cochrane quality rating A* RR 0.97 (0.75, 1.24) P=0.80 (P*het*=0.50)
Incidence of transfusion 11 trials (N=766) *10 trials (N=746)*	219/400 (54.8)	215/366 (58.7)	*Cochrane quality rating B* RR 0.88 (0.75, 1.03) P=0.12 (P*het*=0.04)
Incidence of transfusion 5 trials (N=372)	91/179 (50.8)	88/193 (45.6)	*Cochrane quality rating C* RR 1.11 (0.94, 1.33) P=0.22 (P*het*=0.75)
	Mean ± SD	Mean ± SD	
Units of blood transfused 14 trials (N=885)	NR	NR	*All patients* WMD -0.30 (-0.60, -0.01) P=0.042 (P*het*=0.07)
Units of blood transfused 10 trials (N=621)	NR	NR	*Cardiac surgery* WMD -0.39 (-0.77, -0.01) P=0.047 (P*het*=0.03)

Units of blood transfused 2 trials (N=129)	NR	NR	*Orthopaedic surgery* WMD -0.15 (-0.64, 0.33) P=0.54 (P*het*=0.43)
Units of blood transfused 2 trials (N=135)	NR	NR	*Vascular surgery* WMD 0.06 (-0.89, 1.02) P=0.90 (P*het*=0.40)
Units of blood transfused 10 trials (N=734)	NR	NR	*No autologous techniques used* WMD -0.22 (-0.55, 0.10) P=0.18 (P*het*=0.19)
Units of blood transfused 4 trials (N=151)	NR	NR	*Autologous techniques used* WMD -0.47 (-1.15, 0.20) P=0.17 (P*het*=0.08)
Units of blood transfused 5 trials (N=211)	NR	NR	*Transfused patients* WMD -0.49 (-0.94, -0.04) P=0.033 (P*het*=0.49)
Intraoperative blood loss 7 trials (N=493)	NR	NR	*All surgery* WMD -90.07 (-199.56, 19.42) P=0.11 (P*het*=0.17)
Intraoperative blood loss 3 trials (N=229)	NR	NR	*Cardiac surgery* WMD -119.79 (-314.57, 75.00) P=0.23 (P*het*=0.06)
Postoperative blood loss 18 trials (N=1201)	NR	NR	*All surgery* WMD -92.98 (-149.86, -36.11) P=0.0014 (P*het*=0.001)
Postoperative blood loss 16 trials (N=1107)	NR	NR	*Cardiac surgery* WMD -96.58 (-163.04, -30.12) P=0.0044 (P*het*<0.001)
Postoperative blood loss 1 trial (N=59)	NR	NR	*Cardiac surgery / 0-6 hours post-op* -98.00 (-304.99, 108.99) P=0.35 (P*het*=NA)
Postoperative blood loss 3 trials (N=233)	NR	NR	*Cardiac surgery/ 0-12 hours post-op* WMD -114.05 (-269.46, 41.36) P=0.15 (P*het*=0.004)
Postoperative blood loss 2 trials (N=122)	NR	NR	*Cardiac surgery/ 0-16 hours post-op* WMD -18.01 (-113.34, 77.32) P=0.71 (P*het*=0.42)
Postoperative blood loss 12 trials (N=787)	NR	NR	*All surgery/0-24 hours post-op* WMD -100.41 (-176.48, -24.34) P=0.0097 (P*het*=0.004)
Postoperative blood loss 10 trials (N=693)	NR	NR	*Cardiac surgery/ 0-24 hours post-op* WMD -107.46 (-207.12, -7.80) P=0.035 (P*het*=0.002)
Postoperative + intraoperative blood loss 10 trials (N=669)	NR	NR	*All surgery* WMD -241.78 (-387.55, -96.1) P=0.0012 (P*het*=0.002)
Postoperative + intraoperative blood loss 7 trials (N=496)	NR	NR	*Cardiac surgery* WMD -237.92 (-413.43, -62.40) P=0.0079 (P*het*<0.001)
	n/N (%)	n/N (%)	
Reoperation for bleeding 11 trials (N=778) *9 trials (N=693)*	7/383	14/395	*All surgery* RR 0.69 (0.26, 1.83) P=0.45 (P*het*=0.39)

Mortality 12 trials (N=1061) *8 trials (N=774)*	13/534	7/527	*All surgery* RR 1.72 (0.68, 4.33) P=0.25 (P*het*=0.80)
Myocardial infarction 12 trials (N=876) *9 trials (N=731)*	28/441	18/435	*All surgery* RR 1.38 (0.77, 2.50) P=0.28 (P*het*=0.87)
Stroke (CVA) 5 trials (N=360)	8/184	2/176	*All surgery* RR 2.40 (0.68, 8.43) P=0.17 (P*het*=0.17)
Any thrombosis 9 trials (N=691) *7 trials (N=591)*	14/361	10/330	*All surgery* RR 1.46 (0.64, 3.35) P=0.37 (P*het*=0.78)
Hypotension during infusion requiring treatment 5 trials (N=183)	34/92	9/91	*All surgery* RR 2.81 (1.50, 5.27) P=0.0013 (P*het*=0.50)

Outcome	Clinical importance	Clinical relevance
Desmopressin vs placebo		
Incidence of transfusion	*Any surgery* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cardiac surgery* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Miscellaneous surgery* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cardiac surgery/Primary CABG* 1: Clinically important *benefit*, confidence limit does not include null value. *Cardiac surgery/CABG + valve surgery ± combination/redo surgery* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cardiac surgery/ASA use* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cardiac surgery/no ASA use* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Transfusion protocol* 4: Range of estimates includes clinically important effects but is also compatible with no effect *No transfusion protocol* 4: Range of estimates includes clinically important effects but is also compatible with no effect *No autologous techniques used* 4: Range of estimates includes clinically important effects but is also compatible	1: Patient-relevant clinical outcome.

	with no effect *Autologous techniques used* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cochrane rating A* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cochrane rating B* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cochrane rating C* 4: Range of estimates includes clinically important effects but is also compatible with no effect	
Units of blood transfused	*All surgery/all patients* 1: Clinically important *benefit*, confidence limit does not include null value *Cardiac surgery/all patients* 1: Clinically important *benefit*, confidence limit does not include null value *Orthopaedic surgery/all patients* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Vascular surgery/all patients* 4: Range of estimates includes clinically important effects but is also compatible with no effect *No autologous techniques used/all patients* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Autologous techniques used* 4: Range of estimates includes clinically important effects but is also compatible with no effect *All surgery/transfused patients* 1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Intraoperative blood loss	All surgery 4: Range of estimates includes clinically important effects but is also compatible with no effect Cardiac surgery 4: Range of estimates includes clinically important effects but is also compatible with no effect	

Postoperative blood loss	*All surgery* 1: Clinically important *benefit*, confidence limit does not include null value *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value *Cardiac surgery/0-6 hours post-op* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cardiac surgery/ 0-12 hours post-op* 4: Range of estimates includes clinically important effects but is also compatible with no effect *Cardiac surgery/0-16 hours post-op* 4: Range of estimates includes clinically important effects but is also compatible with no effect *All surgery/0-24 hours/post-op* 1: Clinically important *benefit*, confidence limit does not include null value *Cardiac surgery/0-24 hours post-op* 1: Clinically important *benefit*, confidence limit does not include null value	
Postoperative + intraoperative blood loss	*All surgery* 1: Clinically important *benefit*, confidence limit does not include null value *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value	
Reoperation for bleeding	*All surgery* 4: Range of estimates includes clinically important effects but is also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Mortality	*All surgery* 4: Range of estimates includes clinically important harmful effects but is also compatible with no effect, or a beneficial effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*All surgery* 4: Range of estimates includes clinically important harmful effects but is also compatible with no effect, or a beneficial effect	1: Patient-relevant clinical outcome.
Stroke	*All surgery* 4: Range of estimates includes clinically important harmful effects but is also compatible with no effect, or a beneficial effect	1: Patient-relevant clinical outcome.

Any thrombosis	*All surgery* 4: Range of estimates includes clinically important harmful effects but is also compatible with no effect, or a beneficial effect	1: Patient-relevant clinical outcome.
Hypotension during infusion requiring treatment	*All surgery* 1: Clinically important *harm*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on adults who do not have congenital bleeding disorders undergoing any elective or non-urgent surgery so should be generalisable to other similar patients undergoing similar surgery types.		
Applicability		
The studies in this review were mostly conducted in developed countries (US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and the UK), comparable to Australia. The surgeries performed (and the possible benefits) are likely to be relevant in the Australian context.		
Comments		
This review suggests that desmopressin has no benefit in reducing the requirement for perioperative allogenic RBC transfusion in patients who do not have congenital bleeding disorders. There is some evidence of benefit reduction in perioperative blood loss, but these were small and not considered clinically important.		

Abbreviations: ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CI, confidence interval; CVA, cerebrovascular accident; *het*, heterogeneity; ITT, intention to treat; NA, not applicable; NHMRC, National Health and Medical Research Council; NR, not reported; pRBC, packed red blood cells; RCT, randomised controlled trial; RR, relative risk; SR, systematic review; WMD, weighted mean difference.
a Where individual studies had either 100% events in both treatment arms, no events in both treatment arms or no SD was reported, a risk estimate for that individual study could not be calculated, and it could not be included in the pooled analysis. Where this has occurred, the actual number of studies and subjects included in the analysis will be stated.

STUDY DETAILS				
Citation				
G Crescenzi, G Landoni, G Biondi-Zoccai et al (2008) Desmopressin reduces transfusion needs after surgery. Anesthesiology 109: 1063-1076.				
Affiliation/Source of funds				
Department of Cardiothoracic Anesthesia and Intensive Care, Università Vita-Salute San Raffaele, Milan, Italy; Division of Cardiology, University of Turin, Turin, Italy; Department of Cardiothoracic Anestheia and Intensive Care, IRCCS Policinico S. Donato, San Donato Milanese, Italy. Funding: Solely from institutional and/or departmental sources.				
Study design	Level of evidence	Location/setting		
Systematic review including 42 RCTs (4/38 trials reported data on different patient populations so counted as separate trials hence 42 trials in total) that investigated the effectiveness and safety of desmopressin in patients undergoing surgery.	Level I	Hospital		
Intervention	Comparator			
Desmopressin Dose varied slightly across included studies, being mostly a single 0.3 µg/kg dose administered 15-30 minutes during surgical haemostasis. In six studies the dose was repeated and in 8 studies it was administered immediately before surgery	Placebo			
Population characteristics				
Adult surgical patients.				
Length of follow-up	Outcomes measured			
Not specified	Transfusion (units); blood loss (mL); re-operation for bleeding; incidence of transfusion (blood products); incidence of transfusion (platelets only); hypotension; death; myocardial infarction; thromboses (other than MI).			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all studies. No further details provided.	Baseline characteristics of intervention and control groups not reported. Selection of studies carried out by four reviewers. Data extracted independently by five reviewers. No quality assessment carried out. Analysis of units of blood transfused and blood loss carried out using standardised mean difference. Fixed-effects model used if $I^2 < 50\%$ and random effects model used if $I^2 > 50\%$.	33/38 double blinded.	Publication bias not assessed. Treatment or measurement bias not apparent.	Not stated.
Overall quality assessment (descriptive)				
Fair. The search strategy employed as well as study selection and extraction of data were adequate. No formal quality assessment of included studies was performed. No assessment of reasons for substantial heterogeneity carried out. .				
RESULTS				
Outcome No. trials (N) *No. trials included in analysis (N)*[a]	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)	
Desmopressin vs placebo				

	Mean ± SD	Mean ± SD	
Units of blood products transfused 34 trials (N=2065)	NR	NR	*All studies* SMD -0.29 (-0.52, -0.06) P=0.01 (P*het*<0.001)
Units of blood products transfused 23 trials (N=1607)	NR	NR	*Cardiac surgery* SMD -0.22 (-0.52, 0.08) P=0.14 (P*het*<0.001)
Units of blood products transfused 11 trials (N=458)	NR	NR	*Non-cardiac surgery* SMD -0.45 (-0.77, -0.13) P=0.006 (P*het*=0.003)
Blood loss (mL) 40 trials (N=2445)	NR	NR	*All studies* SMD -0.20 (-0.34, -0.06) P=0.004 (P*het*<0.001)
Blood loss (mL) 29 trials (N=1928)	NR	NR	*Cardiac surgery* SMD -0.23 (-0.40, -0.05) P=0.01 (P*het*<0.001)
Blood loss (mL) 11 trials (N=517)	NR	NR	*Non-cardiac surgery* SMD -0.10 (-0.28, 0.07) P=0.25 (P*het*=0.45)
	n/N (%)	n/N (%)	
Re-operation for bleeding 25 trials (N=1542) *15 trials (N=1186)*	21/763 (2.8)	34/779 (4.4)	*All studies* OR 0.65 (0.39, 1.09) P=0.11 (P*het*=0.50)
Re-operation for bleeding 18 trials (N=1304) *14 trials (N=1136)*	18/647 (2.8)	31/657 (4.7)	*Cardiac surgery* OR 0.63 (0.36, 1.08) P=0.09 (P*het*=0.44)
Re-operation for bleeding 7 trials (N=238) *1 trial (N=50)*	3/116 (2.6)	3/122 (2.5)	*Non-cardiac surgery* OR 1.00 (0.18, 5.51) P=1.0 (P*het*=NA)
Incidence of transfusion with blood products (pRBCs, fresh frozen plasma, platelets) 22 trials (N=1488) *21 trials (N=1429)*	411/746 (55.1)	430/742 (58.0)	*All studies* OR 0.88 (0.70, 1.10) P=0.26 (P*het*=0.19)
Incidence of transfusion with blood products (pRBCs, fresh frozen plasma, platelets) 17 trials (N=1272) *16 trials (N=1213)*	350/638 (54.9)	367/634 (57.9)	*Cardiac surgery* OR 0.87 (0.68, 1.11) P=0.26 (P*het*=0.07)
Incidence of transfusion with blood products (pRBCs, fresh frozen plasma, platelets) 5 trials (N=216)	61/108 (56.5)	63/108 (58.3)	*Non-cardiac surgery* OR 0.93 (0.48, 1.79) P=0.83 (P*het*=0.81)
Incidence of transfusion with platelets 11 trials (N=769)	37/386 (10.0)	53/383 (13.8)	*Cardiac surgery* OR 0.64 (0.41, 1.01) P=0.06 (P*het*=0.22)
Risk of hypotension 18 trials (N=882) *7 trials (N=320)*	37/450 (8.2)	9/432 (2.1)	*All studies* OR 4.84 (2.31, 10.13) P<0.001 (P*het*=0.85)
Risk of hypotension 13 trials (N=717) *5 trials (N=221)*	19/368 (5.2)	1/349 (0.3)	*Cardiac surgery* OR 8.92 (2.54, 31.37) P<0.001 (P*het*=0.94)

Risk of hypotension 5 trials (N=165) *2 trials (N=99)*	18/82 (22.0)	8/83 (9.6)	*Non-cardiac surgery* OR 3.04 (1.18, 7.87) P=0.02 (P*het*=0.64)
Risk of death 23 trials (N=1539) *8 trials (N=673)*	9/771 (1.2)	7/768 (0.9)	*All studies* 1.25 (0.51, 3.04) P=0.63 (P*het*=0.76)
Risk of death 19 trials (N=1334) *7 trials (N=582)*	7/674 (1.0)	7/660 (1.1)	*Cardiac surgery* 1.00 (0.38, 2.62) P=1.00 (P*het*=0.81)
Risk of death 4 trials (N=205) *1 trial (N=50)*	2/97 (2.1)	0/108 (0)	*Non-cardiac surgery* 5.84 (0.27, 125.19) P=0.26 (P*het*=NA)
Risk of myocardial infarction 27 trials (N=1609) *13 trials (N=916)*	31/816 (3.8)	23/793 (2.9)	*All studies* 1.27 (0.73, 2.20) P=0.40 (P*het*=0.88)
Risk of myocardial infarction 19 trials (N=1262) *11 trials (N=775)*	28/648 (4.3)	19/614 (3.1)	*Cardiac surgery* 1.36 (0.75, 2.48) P=0.31 (P*het*=0.86)
Risk of myocardial infarction 8 trials (N=347) *2 trials (N=141)*	3/168 (1.2)	4/179 (2.2)	*Non-cardiac surgery* 0.84 (0.20, 3.53) P=0.81 (P*het*=0.35)
Risk of thromboses (other than myocardial infarction) 26 trials (N=1776) *14 trials (N=1151)*	26/899 (2.9)	22/877 (2.5)	*All studies* 1.20 (0.68, 2.09) P=0.53 (P*het*=0.82)
Risk of thromboses (other than myocardial infarction) 18 trials (N=1400) *11 trials (N=931)*	18/717 (2.5)	14/683 (2.0)	*Cardiac surgery* 1.27 (0.64, 2.50) P=0.49 (P*het*=0.86)
Risk of thromboses (other than myocardial infarction) 8 trials (N=376) *3 trials (N=220)*	8/182 (4.4)	8/194 (4.1)	*Non-cardiac surgery* 1.06 (0.39, 2.84) P=0.92 (P*het*=0.24)

Outcome	Clinical importance	Clinical relevance
Desmopressin vs placebo		
Units of blood transfused	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value. *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect Non-cardiac surgery 1: Clinically important *benefit*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.

Blood loss	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value. *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value. *Non-cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Re-operation for bleeding	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Non-cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Incidence of transfusion with blood products	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Non-cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Incidence of transfusion with platelets	*Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Risk of hypotension	*All studies* 1: Clinically important *harm*, confidence limit does not include null value. *Cardiac surgery* 1: Clinically important *harm*, confidence limit does not include null value. *Non-cardiac surgery* 1: Clinically important *harm*, confidence limit does not include null value.	1: Patient-relevant clinical outcome.

Risk of death	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Non-cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Risk of myocardial infarction	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Non-cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Risk of thromboses (other than myocardial infarction)	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect *Non-cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on patients who have undergone various types of surgery as such it may be relevant to a general surgical population. Subgroup analyses are also provided for cardiac and non-cardiac surgery so these results are likely generalisable to these specific surgical populations.		
Applicability		
This review does not report the locations of the included studies and as such the applicability of the results to the Australian setting is unclear. However, this review include all studies included in a previous Cochrane review which stated the countries in which the included trials were carried out included the US, Canada, Spain, Sweden, Germany, Turkey, Israel, China, Norway, Finland and UK.		
Comments		
This review suggests that desmopressin may slightly reduce blood loss and transfusion volume without reducing the proportion of patients who require transfusion, while increasing the risk of hypotension. The authors note this is due to a mild vasodilating effect of desmopressin and does not result in changes in filling pressure, heart rate or right ventricular function.		

Abbreviations: CI, confidence interval; *het*, heterogeneity; ITT, intention to treat; MI, myocardial infarction; OR, odds-ratio; pBRC, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; SMD, standardised mean difference.

[a] Where individual studies had either 100% events in both treatment arms, no events in both treatment arms or no SD was reported, a risk estimate for that individual study could not be calculated, and it could not be included in the pooled analysis. Where this has occurred, the actual number of studies and subjects included in the analysis will be stated.

STUDY DETAILS				
Citation				
KS Gurusamy, D Sharma, BR Davidson (2009) Pharmacological interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database of Systematic Reviews. 009,Issue 4.Art.No.: CD008085. DOI:10.1002/14651858. CD008085.				
Affiliation/Source of funds				
University Department of Surgery, Royal Free College and University College School of Medicine, London, UK Funding: None				
Study design	Level of evidence	Location/setting		
Systematic review including 6 trials (1 aprotinin, 1 tranexamic acid, 1 aminocaproic acid; 3 non-relevant interventions) that investigated the effectiveness of pharmacological interventions to reduce blood loss and transfusion requirements in patients undergoing liver resection.	Level I	Hospital		
Intervention	Comparator			
Tranexamic acid, aprotinin, desmopressin, recombinant factor VIIa, antithrombin III	No treatment, placebo or active			
Population characteristics				
Patients undergoing liver resection				
Length of follow-up	Outcomes measured			
Not specified	Perioperative mortality; survival; liver failure; perioperative morbidity; transfusion requirements; operating time; hospital stay; intensive therapy unit; blood loss; liver function; biochemical markers of liver injury			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
All trials randomised. 2/3 trials had adequate sequence generation and 3/3 trials inadequately reported allocation concealment	1 trial free of baseline imbalance, 2 trials unclear Studies included and data extracted independently by two reviewers. Risk of bias assessed by two reviewers. Meta-analysis methods as per the Cochrane Collaboration. Only one trials for each comparison.	3 studies adequately blinded	Publication bias not assessed. Treatment or measurement bias not apparent.	Some patients excluded from analysis of efficacy in included studies (12/109 aprotinin study; 3/217 tranexamic acid; 0/60 desmopressin)
Overall quality assessment (descriptive)				
Good. Comprehensive literature search carried out. Quality assessment undertaken. Single study only available for each comparison. Authors note all studies at high risk of bias.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)	
Aprotinin vs placebo				
	n/N (%)	n/N (%)		
Mortality 1 trial (N=37)	2/17	2/20	RR 1.18 (0.18, 7.48) P=0.86 (P*het*=NA)	

Incidence of blood transfusion 1 trial (N=97)	8/48	19/49	RR 0.43 (0.21, 0.89) P=0.02 (P*het*=NA)
	Mean ± SD	Mean ± SD	
Operating time (mins) 1 trial (N=97)	232 ± SD 75	233 ± SD 71	MD -1.00 (-30.08, 28.08) P=0.95 (Phet=NA)
Operative blood loss (mL) 1 trial (N=97)	1217 ± SD 966	1653 ± 1221	MD -436.00 (-873.67, 1.67) P=0.05 (P*het*=NA)
Tranexamic acid vs placebo			
	n/N (%)	n/N (%)	
Mortality 1 trial (N=217)	0/109	0/108	RR 0.0 (0.0, 0.0)
Incidence of blood transfusion 1 trial (N=214)	0/108	17/106	RR 0.03 (0.00, 0.46) P=0.01 (P*het*=NA)
	Mean ± SD	Mean ± SD	
Operating time (mins) 1 trial (N=214)	253.8 ± SD 126.7	306 ± 126.7	MD -52.20 (-86.15, -18.25) P=0.003 (P*het*=NA)
Hospital stay (days) 1 trial (N=NR)	8 ± 7.66	9 ± 7.66	MD NR P=0.34 (P*het*=NA)
Transection blood loss (mL) 1 trial (N=214)	190 ± 653	450 ± 653	MD -260.00 (-434.99, -85.01) P=0.0036 (P*het*=NA)
Operative blood loss (mL) 1 trial (N=214)	300 ± SD 754	600 ± SD 754	MD -300.00 (-502.05, -97.95) P=0.0036 (P*het*=NA)
Desmopressin vs placebo			
	n/N (%)	n/N (%)	
Incidence of blood transfusion 1 trial (N=59)	3/30 (10.0%)	5/29 (17.2%)	RR 0.58 (0.15, 2.21) P=0.42 (P*het*=NA)
Red cell transfusion (units) 1 trial (N=59)	0.23 ± SD 0.82	0.72 ± 2.09	SMD -0.31 (-0.82, 0.21) P=0.24 (P*het*=NA)
	Mean ± SD	Mean ± SD	
Operating time (minutes) 1 trial (N=59)	405 ± 162	435 ± 162	MD -30.00 (-112.69, 52.69) P=0.48 (P*het*=NA)
Transection blood loss (mL) 1 trial (N=59)	405 ± 1140	450 ± 1140	MD -45.00 (-626.86, 536.86) P=0.88 (P*het*=NA)
Operative blood loss (mL) 1 trial (N=59)	832.5 ± 1426.7	800 ± 1426.7	MD 32.50 (-695.69, 760.69) P=0.93 (P*het*=NA)

Outcome	Clinical importance	Clinical relevance
Aprotinin vs placebo		
Mortality	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Incidence of blood transfusion	1: Clinically important *benefit*, confidence limit does not include null value (p=0.02)	1: Patient-relevant clinical outcome.
Operating time (mins)	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Operative blood loss (mL)	2: Point estimate indicates clinically important effects, but range of estimates also compatible with no clinically important effect (p=0.05)	1: Patient-relevant clinical outcome.
Tranexamic acid vs placebo		

Mortality	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Incidence of blood transfusion	1: Clinically important *benefit*, confidence limit does not include null value (p=0.01)	1: Patient-relevant clinical outcome.
Operating time (mins)	1: Clinically important *benefit*, confidence limit does not include null value (p=0.01)	2: Predictive surrogate outcome.
Hospital stay (days)	4: Range of estimates includes clinically important effects, but also compatible with no effect	2: Predictive surrogate outcome.
Transection blood loss (mL)	1: Clinically important *benefit*, confidence limit does not include null value (p=0.0036)	1: Patient-relevant clinical outcome.
Operative blood loss (mL)	1: Clinically important *benefit*, confidence limit does not include null value (p=0.0036)	1: Patient-relevant clinical outcome.
Desmopressin vs placebo		
Incidence of blood transfusion	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Red cell transfusion (units)	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Operating time (minutes)	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
Transection blood loss (mL)	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Operative blood loss (mL)	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on patients who have undergone liver transection so may be generalisable only to this specific surgery group.		
Applicability		
This review does not report the locations of the included studies and as such the applicability of the results to the Australian setting is unclear.		
Comments		
The authors conclude that none of the included interventions seem to decrease perioperative morbidity or offer long-term survival benefit. Aprotinin and tranexamic seem to reduce blood transfusion requirements however as the data is based on few trials and small sample sizes the results should be interpreted with caution.		

Abbreviations: CI, confidence interval; het, heterogeneity; ITT, intention to treat; MD, mean difference; NA, not applicable; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; SMD, standardised mean difference.

<table>
<tr><td colspan="4">STUDY DETAILS</td></tr>
<tr><td colspan="4">Citation</td></tr>
<tr><td colspan="4">DA Henry, PA Carless, AJ Moxey et al (2007) Antifibrinolytic use for minimising perioperative allogenic blood transfusion. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD001886. DOI: 10.1002/14651858.CD001886.pub2.</td></tr>
<tr><td colspan="4">Affiliation/Source of funds</td></tr>
<tr><td colspan="4">Institute of Clinical Evaluative Sciences, Toronto, Canada; Discipline of Clinical Pharmacology, Faculty of Health, University of Newcastle, Newcastle, Australia; Cancer Epidemiology Research Unit, The Cancer Council NSW, Sydney, Australia; Scottish National Blood Transfusion Service, Edinburgh, UK; Department of Medicine, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Canada; Ottawa Health Research Institute, University of Ottawa Centre for Transfusion Research, Ottawa, Canada.
Funding: Special purpose grant, Hunter Area Pathology Service, Australia (Internal grant); Australian Health Minister's Advisory Committee. NHMRC, Australia.</td></tr>
<tr><td>Study design</td><td colspan="2">Level of evidence</td><td>Location/setting</td></tr>
<tr><td>Systematic review including 211 placebo-controlled and head-to-head trials (116 aprotinin, 45 tranexamic acid and 11 aminocaproic acid) that investigated the effectiveness and safety of pharmacological interventions for minimising perioperative allogenic blood transfusion.</td><td colspan="2">Level I</td><td>Hospital</td></tr>
<tr><td colspan="2">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="2">Aprotinin, tranexamic acid, ε-aminocaproic acid</td><td colspan="2">Placebo/no treatment or active</td></tr>
<tr><td colspan="4">Population characteristics</td></tr>
<tr><td colspan="4">Adult surgical patients (or patients < 18 years if undergoing a procedure predominantly performed in adults)</td></tr>
<tr><td colspan="2">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="2">Not specified</td><td colspan="2">Primary outcomes:
Proportion of patients transfused with allogenic blood, autologous blood, or both; amount of allogenic and autologous blood transfused; perioperative blood loss.
Secondary outcomes:
Re-operation due to bleeding; mortality; postoperative complications (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, any thrombosis, renal failure); length of hospital stay.</td></tr>
</table>

INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
All trials randomised. 56 trials had adequate allocation method and remaining trials did not. 32% judged to have adequate concealment, 14% did not have adequate concealment and 53% were not adequately described.	Comparison of baseline characteristics not assessed. Studies included and data extracted independently by at least two reviewers. Risk of bias assessed by two reviewers. (note: 16 trials not assessed for quality by both reviewers) Meta-analysis methods as per the Cochrane Collaboration.	70% trials double-blind, 7% double-blind but method unclear, 24% not double-blind	Possible evidence of publication bias particularly with aprotinin trials but further investigation revealed unlikely to overestimate results and not produce a false-positive result.	45% of trials reported no exclusions or used ITT, 37% exclusions were judged not likely to cause bias, 17% exclusions judged excessive and likely to cause bias, or not reported.
Overall quality assessment (descriptive)				
Good. Comprehensive literature search carried out. Quality assessment undertaken. Subgroup analyses performed on *a priori* categories including surgery, transfusion protocol, dose and trial quality.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)	
Aprotinin vs placebo/no treatment				
Exposed to allogenic blood				
	n/N (%)	n/N (%)		
99 trials (N=10,144) *96 trials (N=9949)*[a]	2521/5750 (43.8)	2827/4394 (64.3)	*All studies* RR 0.66 (0.62, 0.71) P<0.001 (P*het*<0.001)	
77 trials (N=8837) *76 trials (N=8793)*	2279/5003 (45.6)	2535/3834 (66.1)	*Cardiac surgery* RR 0.66 (0.61, 0.72) P<0.001 (P*het*<0.001)	
14 trials (N=794) *13 trials (N=771)*	111/480 (23.1)	138/314 (43.9)	*Orthopaedic surgery* RR 0.69 (0.56, 0.85) P<0.001 (P*het*=0.23)	
2 trials (N=62)	4/30 (13.3)	16/32 (50.0)	*Thoracic surgery* RR 0.28 (0.11, 0.74) P=0.011(P*het*=0.54)	
2 trials (N=188) *1 trial (N=60)*	94/105 (89.5)	77/83 (92.8)	*Vascular surgery* RR 1.01 (0.72, 1.40) P=0.98 (P*het*=1.00)	
2 trials (N=177)	21/87 (24.1)	39/90 (43.3)	*Liver surgery* RR 0.58 (0.37, 0.90) P=0.015 (Phet=0.31)	
1 trial (N=56)	11/30 (36.7)	13/26 (50.0)	*Neuro surgery* RR 0.73 (0.40, 1.35) P=0.32 (P*het*=NA)	
1 trial (N=30)	1/15 (6.7)	9/15 (60.0)	*Orthognathic surgery* 0.11 (0.02, 0.77) P=0.026 (P*het*=NA)	
16 trials (N=1251)	345/649 (53.2)	394/602 (65.4)	*Prime dose* RR 0.83 (0.71, 0.96) P=0.014 (P*het*<0.001)	

46 trials (N=3268) *43 trials (N=3073)*	648/1733 (37.4)	882/1535 (57.5)	*Low dose* RR 0.66 (0.59, 0.74) P<0.001 (P*het*<0.001)
56 trials (N=6569)	1522/3320 (45.8)	2204/3249 (67.8)	*High dose* RR 0.65 (0.60, 0.71) P<0.001 (P*het*<0.001)
15 trials (N=1191)	317/610 (52.0)	379/581 (65.2)	*Cardiac surgery and prime dose* RR 0.81 (0.69, 0.96) P=0.012 (P*het*<0.001)
25 trials (N=2039) *24 trials (N=1995)*	438/1043 (42.0)	605/996 (60.7)	*Cardiac surgery and low dose* RR 0.67 (0.58, 0.77) P<0.001 (P*het*<0.001)
55 trials (N=6533)	1518/3302 (46.0)	2193/3231 (67.9)	*Cardiac surgery and high dose* RR 0.66 (0.60, 0.72) P<0.001 (*Phet*<0.001)
Units of allogenic blood transfused			
	Mean ± SD	Mean ± SD	
63 trials (N=6820)	NR	NR	*All patients* WMD -1.07 (-1.31, -0.83) P<0.001 (P*het*<0.001)
38 trials (N=3388) *35 trials (N=3363)*	NR	NR	*Transfused patients* WMD -0.96 (-1.24, -0.68) P<0.001 (P*het*<0.001)
Blood loss (total)			
	Mean ± SD	Mean ± SD	
15 trials (N=1577)	NR	NR	*All studies* WMD -414.48 (-520.13, -308.82) P<0.001 (P*het*=0.003)
5 trials (N=1147)	NR	NR	*Cardiac surgery* WMD -489.06 (-571.32, -406.80) P<0.001 (P*het*=0.62)
10 trials (N=430)	NR	NR	*Orthopaedic surgery* WMD -399.09 (-562.81, -235.37) P<0.001 (P*het*=0.01)
Blood loss (intraoperative)			
	Mean ± SD	Mean ± SD	
13 trials (N=722)	NR	NR	*All studies* WMD -185.32 (-280.23, -90.41) P<0.001 (P*het*<0.001)
5 trials (N=360)	NR	NR	*Cardiac surgery* WMD -140.00 (-244.42, -35.59) P=0.0086 (P=0.01)
5 trials (N=201)	NR	NR	*Orthopaedic surgery* WMD -151.05 (-317.63, 15.52) P=0.076 (P*het*=0.16)
1 trial (N=24)	NR	NR	*Thoracic surgery* WMD -532.0 (-863.00, -199.00) P=0.0016 (P*het*=NA)
2 trials (N=137)	NR	NR	*Liver surgery* WMD -1200.40 (-2943.39, -542.59) P=0.18 (P*het*=0.02)
Blood loss (postoperative)			
	Mean ± SD	Mean ± SD	
79 trials (N=7414)	NR	NR	*All studies* WMD -358.-403.64, -312.62) P<0.001 (P*het*<0.001)

68 trials (N=6948)	NR	NR	*Cardiac surgery* WMD -385.43 (-432.36, -338.50) P<0.001 (P*het*<0.001)
7 trials (N=318)	NR	NR	*Orthopaedic surgery* WMD -113.58 (-223.69, -3.46) P=0.043 (P*het*=0.005)
1 trial (N=24)	NR	NR	*Thoracic surgery* WMD -441.0 (-786.40, -95.60) P=0.012 (P*het*=NA)
1 trial (N=30)	NR	NR	*Orthognathic surgery* WMD -513.0 (-717.21, -308.79) P<0.001 (P*het*=NA)
1 trial (N=44)	NR	NR	*Liver surgery* WMD -105.0 (-194.36, -15.64) P=0.021 (P*het*=NA)
1 trial (N=50)	NR	NR	*Vascular surgery* WMD -203.00 (-404.93, -1.07) P=0.049 (P*het*=NA)
15 trials (N=1158)	NR	NR	*Cardiac surgery and prime dose* WMD -343.08 (-458.13, -228.04) P<0.001 (P*het*<0.001)
21 trials (N=1781)	NR	NR	*Cardiac surgery and low dose* WMD -293.24 (-348.67, -237.81) P<0.001 (P*het*<0.001)
48 trials (N=4819)	NR	NR	*Cardiac surgery and high dose* WMD -428.09 (-485.38, -370.80) P<0.001 (P*het*<0.001)
Re-operation for bleeding			
	n/N (%)	n/N (%)	
51 trials (N=5384) *36 trials (N=4715)*	58/3030 (1.9)	110/2354 (4.7)	*All trials* RR 0.48 (0.35, 0.68) P<0.001 (P*het*=0.51)
47 trials (N=5153) *33 trials (N=4534)*	55/2915 (1.9)	101/2238 (4.5)	*Cardiac surgery* RR 0.49 (0.34, 0.70) P<0.001 (P*het*=0.41)
Mortality			
	n/N (%)	n/N (%)	
52 trials (N=7721) *37 trials (N=6645)*	105/4319 (2.4)	87/3402 (2.6)	*All trials* RR 0.90 (0.67, 1.20) P=0.47 (P*het*=0.95)
45 trials (N=7078) *31 trials (N=6058)*	99/3907 (2.5)	77/3171 (2.4)	*Cardiac surgery* RR 0.95 (0.70, 1.28) P=0.72 (P*het*=0.93)
Myocardial infarction			
	n/N (%)	n/N (%)	
40 trials (N=6107) *34 trials (N=5758)*	153/3523 (4.3)	118/2584 (4.6)	*All trials* RR 0.92 (0.72, 1.18) P=0.50 (P*het*=0.91)
37 trials (N=5628) *31 trials (N=5279)*	152/3204 (4.7)	113/2424 (4.7)	*Cardiac surgery* RR 0.95 (0.74, 1.22) P=0.69 (P*het*=0.92)
Stroke			
	n/N (%)	n/N (%)	
16 trials (N=2298) *14 trials (N=2158)*	16/1458 (1.1)	14/840 (1.7)	*All trials* RR 0.78 (0.38, 1.62) P=0.51 (P*het*=0.71)

11 trials (N=1303) *9 trials (N=1163)*	10/773 (1.3)	10/530 (1.9)	*Cardiac surgery* RR 0.76 (0.30, 1.93) P=0.57 (P*het*=0.40)
Deep vein thrombosis			
	n/N (%)	n/N (%)	
15 trials (N=1104) *11 trials (N=986)*	36/679 (5.3)	23/425 (5.4)	*All trials* RR 0.79 (0.46, 1.34) P=0.38 (P*het*=0.80)
2 trials (N=272)	4/170 (2.4)	1/102 (1.0)	*Cardiac surgery* RR 2.52 (0.41, 15.45) P=0.32 (P*het*=0.71)
Pulmonary embolism			
	n/N (%)	n/N (%)	
3 trials (N=233) *2 trials (N=175)*	4/129 (3.1)	2/104 (1.9)	*All trials* RR 1.98 (0.38, 10.46) P=0.42 (P*het*=0.95)
Other thrombosis			
	n/N (%)	n/N (%)	
9 trials (N=736) *7 trials (N=583)*	5/402 (1.2)	8/334 (2.4)	*All trials* RR 0.73 (0.25, 2.15) P=0.57 (P*het*=0.64)
4 trials (N=426) *3 trials (N=370)*	2/245 (0.8)	4/181 (2.2)	*Cardiac surgery* RR 0.62 (0.11, 3.36) P=0.58 (P*het*=0.50)
Coronary artery graft occlusion			
	n/N (%)	n/N (%)	
2 trials (N=728)	54/369 (14.6)	39/359 (10.9)	*Cardiac surgery* RR 0.76 (0.10, 5.67) P=0.79 (P*het*=0.13)
Renal failure/dysfunction			
	n/N (%)	n/N (%)	
21 trials (N=4412) *14 trials (N=3908)*	75/2525 (3.0)	42/1887 (2.2)	*All trials* RR 1.16 (0.79, 1.70) P=0.46 (P*het*=0.88)
18 trials (N=4174) *11 trials (N=3670)*	68/2395 (2.9)	39/1779 (2.2)	*Cardiac surgery* RR 1.12 (0.74, 1.67) P=0.60 (P*het*=0.85)
Hospital length of stay (days)			
	Mean ± SD	Mean ± SD	
17 trials (N=1570)	NR	NR	*All trials* WMD -0.01 (-0.50, 0.48) P=0.96 (P*het*=0.19)
13 trials (N=1412)	NR	NR	*Cardiac surgery* WMD -0.10 (-0.64, 0.44) P=0.73 (P*het*=0.12)
Tranexamic acid vs placebo			
Exposed to allogenic blood			
	n/N (%)	n/N (%)	
53 trials (N=3836) *51 trials (N=3751)*	546/2020 (27.0)	796/1816 (43.8)	*All trials* RR 0.61 (0.54, 0.70) P<0.001 (P*het*<0.001)
29 trials (N=2488) *28 trials (N=2443)*	367/1322 (27.8)	476/1166 (40.8)	*Cardiac surgery* RR 0.69 (0.60, 0.79) P<0.001 (P*het*=0.03)

21 trials (N=993) *20 trials (N=953)*	139/520 (26.7)	247/473 (52.2)	*Orthopaedic surgery* RR 0.44 (0.33, 0.60) P<0.001 (P*het*<0.001)
2 trials (N=296)	29/148 (19.6)	54/148 (36.5)	*Liver surgery* RR 0.16 (0.00, 32.47) P=0.50 (P*het*<0.001)
1 trial (N=59)	11/30 (36.7)	19/29 (65.5)	*Vascular surgery* RR 0.56 (0.33, 0.96) P=0.035 (P*het*=NA)
16 trials (N=926)	162/495 (32.7)	204/431 (47.3)	*Cardiac surgery/total dose < 2.0 g* RR 0.72 (0.59, 0.88) P=0.0013 (P*het*=0.05)
14 trials (N=1616) *13 trials (N=1571)*	205/827 (24.8)	286/789 (36.2)	*Cardiac surgery/total dose 2-10 g* RR 0.67 (0.55, 0.83) P<0.001 (P*het*=0.09)
Units of allogenic blood transfused			
	Mean ± SD	Mean ± SD	
16 trials (N=1071) *14 trials (N=965)*	NR	NR	*All patients* WMD -1.12 (-1.59, -0.64) P<0.001 (P*het*<0.001)
11 trials (N=429)	NR	NR	*Transfused patients* WMD -0.51 (-1.06, 0.04) P=0.071 (P*het*<0.001)
Blood loss (total)			
	Mean ± SD	Mean ± SD	
18 trials (N=955)	NR	NR	*All studies* WMD -443.53 (-572.08, -314.98) P<0.001 (P*het*<0.001)
3 trials (N=245)	NR	NR	*Cardiac surgery* WMD -439.82 (-606.50, -273.15) P<0.001 (P*het*=0.82)
14 trials (N=690)	NR	NR	*Orthopaedic surgery* WMD -439.51 (-590.93, -288.09) P<0.001 (P*het*<0.001)
1 trial (N=20)	NR	NR	*Liver surgery* WMD -6552.0 (-14329.54, 1225.54) P=0.099 (P*het*=NA)
Blood loss (intraoperative)			
	Mean ± SD	Mean ± SD	
10 trials (N=553)	NR	NR	*All studies* WMD -54.89 (-105.31, -4.48) P=0.033 (P*het*=0.26)
3 trials (N=144)	NR	NR	*Cardiac surgery* WMD -287.16 (-481.57, -92.75) P=0.0038 (P*het*=0.66)
7 trials (N=409)	NR	NR	*Orthopaedic surgery* WMD -29.52 (-69.17, 10.14) P=0.14 (P*het*=0.69)
Blood loss (postoperative)			
	Mean ± SD	Mean ± SD	
23 trials (N=1423)	NR	NR	*All studies* WMD -247.90 (-313.07, -182.73) P<0.001 (P*het*<0.001)

17 trials (N=1130)	NR	NR	*Cardiac surgery* WMD -262.60 (-318.62, -206.59) P<0.001 (P*het*=0.01)
6 trials (N=293)	NR	NR	*Orthopaedic surgery* WMD -209.72 (-384.28, -35.16) P=0.019 (P*het*<0.001)
9 trials (N=302)	NR	NR	*Cardiac surgery/total dose < 2.0 g* WMD -251.77 (-352.27, -151.26) P<0.001 (P*het*=0.07)
8 trials (N=828)	NR	NR	*Cardiac surgery/total dose 2.0-10.0 g* WMD -272.85 (-340.79, -204.90) P<0.001 (P*het*=0.03)
Re-operation for bleeding			
	n/N (%)	n/N (%)	
20 trials (N=1676) *18 trials (N=1598)*	25/872 (2.9)	40/804 (5.0)	*All studies* RR 0.67 (0.41, 1.09) P=0.11 (P*het*=0.92)
19 trials (N=1618) *17 trials (N=1540)*	23/843 (2.7)	38/775 (4.9)	*Cardiac surgery* RR 0.65 (0.39, 1.08) P=0.097 (P*het*=0.90)
Mortality			
	n/N (%)	n/N (%)	
24 trials (N=2210) *16 trials (N=1684)*	14/1129 (1.2)	26/1081 (2.4)	*All studies* RR 0.60 (0.32, 1.12) P=0.11 (P*het*=0.84)
18 trials (N=1702) *11 trials (N=1390)*	8/872 (0.9)	16/830 (1.9)	*Cardiac surgery* RR 0.55 (0.24, 1.25) P=0.15 (P*het*=0.73)
Myocardial infarction			
	n/N (%)	n/N (%)	
17 trials (N=1718) *12 trials (N=1344)*	15/885 (1.7)	16/833 (1.9)	*All studies* RR 0.96 (0.48, 1.90) P=0.91 (P*het*=0.96)
15 trials (N=1632) *9 trials (N=1048)*	13/841 (1.5)	15/791 (1.9)	*Cardiac surgery* 0.91 (0.44, 1.88) P=0.79 (P*het*=0.91)
Stroke			
	n/N (%)	n/N (%)	
14 trials (N=1403) *7 trials (N=937)*	10/740 (1.4)	7/663 (1.1)	*All studies* RR 1.25 (0.47, 3.31) P=0.65 (P*het*=0.79)
13 trials (N=1345) *5 trials (N=841)*	9/711 (1.3)	5/634 (0.8)	*Cardiac surgery* RR 1.52 (0.52, 4.41) P=0.44 (P*het*=0.78)
Deep vein thrombosis			
	n/N (%)	n/N (%)	
18 trials (N=1109) *10 trials (N=681)*	11/565 (1.9)	16/544 (2.9)	*All studies* RR 0.77 (0.37, 1.61) P=0.49 (P*het*=0.81)
4 trials (N=442) *2 trials (N=291)*	0/221 (0.0)	2/201 (1.0)	*Cardiac surgery* RR 0.37 (0.04, 3.47) P=0.38 (P*het*=0.95)
Pulmonary embolism			
	n/N (%)	n/N (%)	

13 trials (N=946) *7 trials (N=568)*	2/487 (0.4)	6/459 (1.3)	*All studies* RR 0.55 (0.17, 1.76) P=0.31 (P*het*=0.93)
6 trials (N=569) *2 trials (N=289)*	0/298 (0.0)	2/271 (0.7)	*Cardiac surgery* RR 0.33 (0.04, 3.15) P=0.34 (P*het*=0.98)
Other thrombosis			
	n/N (%)	n/N (%)	
7 trials (N=289) *2 trials (N=114)*	5/148 (3.4)	2/141 (1.4)	*All studies* RR 2.10 (0.49, 8.99) P=0.32 (P*het*=0.80)
Renal failure/dysfunction			
	n/N (%)	n/N (%)	
5 trials (N=444) *4 trial (N=400)*	2/222 (0.9)	3/222 (1.4)	*Cardiac surgery* RR 0.73 (0.16, 3.32) P=0.68 (P*het*=0.69)
Hospital length of stay			
	Mean ± SD	Mean ± SD	
4 trials (N=176)	NR	NR	*All studies* RR -0.30 (-0.71, 0.10) P=0.14 (P*het*=0.66)
2 trials (N=116)	NR	NR	*Cardiac surgery* RR -0.23 (-0.67, 0.21) P=0.31 (P*het*=0.64)
E-aminocaproic acid vs placebo			
Exposed to allogenic blood			
	n/N (%)	n/N (%)	
14 trials (N=801)	138/414 (33.3)	173/387 (44.7)	*All studies* RR 0.75 (0.58, 0.96) P=0.023 (P*het*=0.03)
10 trials (N=597)	82/313 (26.2)	113/284 (39.8)	*Cardiac surgery* RR 0.65 (0.47, 0.91) P=0.011 (P*het*=0.11)
3 trials (N=122)	20/59 (33.9)	23/63 (36.5)	*Orthopaedic surgery* RR 0.96 (0.61, 1.50) P=0.85 (P*het*=0.64)
1 trial (N=82)	36/42 (85.7)	37/40 (92.5)	*Liver surgery* RR 0.93 (0.80, 1.08) P=0.33 (P*het*=NA)
Units of allogenic blood transfused			
	Mean ± SD	Mean ± SD	
4 trials (N=198)	NR	NR	*All patients* WMD -1.77 (-2.59, -0.95) P<0.001 (P*het*=0.02)
3 trials (N=119)	NR	NR	*Transfused patients* WMD 0.22 (-0.34, 0.79) P=0.44 (P*het*=0.76)
Blood loss (total)			
	Mean ± SD	Mean ± SD	
2 trials (N=92)	NR	NR	*Orthopaedic surgery* WMD -299.69 (-522.54, -76.84) P=0.0084 (P*het*=0.39)
Blood loss (intraoperative)			
	Mean ± SD	Mean ± SD	

4 trials (N=171)	NR	NR	*All studies* WMD -142.02 (-284.95, 0.92) P=0.051 (P*het*=0.19)
2 trials (N=79)	NR	NR	*Cardiac surgery* WMD -213.58 (-310.03, -117.13) P<0.001 (P*het*=0.73)
2 trials (N=92)	NR	NR	*Orthopaedic surgery* WMD 10.94 (-259.66, 281.54) P=0.94 (P*het*=0.26)
Blood loss (postoperative)			
	Mean ± SD	Mean ± SD	
12 trials (N=940)	NR	NR	*All studies* WMD -202.08 (-273.64, -130.53) P<0.001 (P*het*<0.001)
11 trials (N=894)	NR	NR	*Cardiac surgery* WMD -196.27 (-271.75, -120.79) P<0.001 (P*het*<0.001)
1 trial (N=46)	NR	NR	*Orthopaedic surgery* WMD -276.00 (-448.83, -103.17) P=0.0017 (P*het*=NA)
Re-operation for bleeding			
	n/N (%)	n/N (%)	
7 trials (N=740) *5 trials (N=662)*	3/379 (0.8)	12/361 (3.3)	*Cardiac surgery* RR 0.35 (0.11, 1.17) P=0.087 (P*het*=0.78)
Mortality			
	n/N (%)	n/N (%)	
6 trials (N=754) *5 trials (N=714)*	10/388 (2.6)	7/366 (1.9)	*All studies* RR 1.17 (0.47, 2.93) P=0.73 (P*het*=0.78)
5 trials (N=672) *4 trials (N=632)*	7/346 (2.0)	3/326 (0.9)	*Cardiac surgery* RR 1.65 (0.50, 5.43) P=0.41 (P*het*=0.81)
Myocardial infarction			
	n/N (%)	n/N (%)	
5 trials (N=662) *4 trials (N=632)*	12/340 (3.5)	4/322 (1.2)	*Cardiac surgery* RR 0.89 (0.37, 2.18) P=0.80 (P*het*=0.33)
Stroke			
	n/N (%)	n/N (%)	
6 trials (N=702) *3 trials (N=541)*	2/361 (0.6)	3/341 (0.9)	*Cardiac surgery* RR 0.59 (0.10, 3.44) P=0.55 (P*het*=0.47)
Deep vein thrombosis			
	n/N (%)	n/N (%)	
3 trials (N=122) *1 trial (N=46)*	3/59 (5.1)	3/63 (4.8)	*All studies* RR 1.09 (0.25, 4.85) P=0.91 (P*het*=1.00)
Pulmonary embolism			
	n/N (%)	n/N (%)	
2 trials (N=92) *1 trial (N=46)*	0/44 (0.0)	1/48 (2.1)	*All studies* RR 0.36 (0.02, 8.46) P=0.53 (P*het*=1.00)
Other thrombosis			
	n/N (%)	n/N (%)	

1 trial (N=82)	2/42 (4.8)	2/40 (5.0)	*All studies* RR 0.95 (0.14, 6.44) P=0.96 (P*het*=NA)
Hospital length of stay			
	Mean ± SD	Mean ± SD	
1 trial (N=46)	11.9 ± 7.3	9 ± 5.9	*All studies* MD 2.90 (-0.96, 6.76) P=0.14 (P*het*=NA)

Outcome	Clinical importance	Clinical relevance
Aprotinin vs placebo		
Exposed to allogenic blood	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and prime dose* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.014) *Cardiac surgery and low dose* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and high dose* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Orthopaedic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Thoracic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.011) *Vascular surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Liver surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.015) *Neuro surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Orthognathic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.026)	1: Patient-relevant clinical outcome.
Units of allogenic blood transfused	*All patients* 1: Clinically important *benefit*,	1: Patient-relevant clinical outcome.

	confidence limit does not include null value (p<0.001) *Transfused patients* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	
Blood loss (total)	All studies 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) Cardiac surgery 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) Orthopaedic surgery 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.
Blood loss (intraoperative)	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0086) *Orthopaedic surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Thoracic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0016) *Liver surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.
Blood loss (postoperative)	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and prime dose* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and low dose* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and high dose* 1: Clinically important *benefit*, confidence limit does not include null	1: Patient-relevant clinical outcome.

	value (p<0.001) *Orthopaedic surgery* 2: Clinically important *benefit*, but confidence limit may include non-clinically important benefit (p=0.043) *Thoracic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.012) *Orthognathic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Liver surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.021) *Vascular surgery* 2: Clinically important *benefit*, but confidence limit may include non-clinically important benefit (p=0.049)	
Re-operation for bleeding	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.
Mortality	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Stroke	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Deep vein thrombosis	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.

	Cardiac surgery 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	
Pulmonary embolism	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Other thrombosis	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Coronary artery graft occlusion	*Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Renal failure/dysfunction	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Hospital length of stay	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
Tranexamic acid vs placebo		
Exposed to allogenic blood	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and dose <2.0 g* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0013) *Cardiac surgery and dose 2-10 g* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Orthopaedic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.

	Vascular surgery 1: Clinically important *benefit*, confidence limit does not include null value (p=0.035) *Liver surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	
Units of allogenic blood transfused	*All patients* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Transfused patients* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Blood loss (total)	All studies 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) Cardiac surgery 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) Orthopaedic surgery 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Liver surgery* 4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Blood loss (intraoperative)	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.033) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0038) *Orthopaedic surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Blood loss (postoperative)	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and dose < 2 g* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Cardiac surgery and dose 2-10 g*	1: Patient-relevant clinical outcome.

	1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Orthopaedic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.019)	
Re-operation for bleeding	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Mortality	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Stroke	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Deep vein thrombosis	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Pulmonary embolism	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Other thrombosis	*All studies* 4: Range of estimates includes clinically	1: Patient-relevant clinical outcome.

	important effects, but also compatible with no or harmful effect	
Renal failure/dysfunction	*Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Hospital length of stay	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
E-aminocaproic acid vs placebo		
Exposed to allogenic blood	*All studies* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.023) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.011) *Orthopaedic surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Liver surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Units of allogenic blood transfused	*All patients* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Transfused patients* 4: Range of estimates includes clinically important effects, but also compatible with no effect.	1: Patient-relevant clinical outcome.
Blood loss (total)	*Orthopaedic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0084)	1: Patient-relevant clinical outcome.
Blood loss (intraoperative)	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no effect. *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Orthopaedic surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Blood loss (postoperative)	*All studies* 1: Clinically important *benefit*,	1: Patient-relevant clinical outcome.

	confidence limit does not include null value (p<0.001) *Cardiac surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Orthopaedic surgery* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0017)	
Re-operation for bleeding	*Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Mortality	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Stroke	*Cardiac surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Deep vein thrombosis	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Pulmonary embolism	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Other thrombosis	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Hospital length of stay	*All studies* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on patients who have undergone many different types on surgery so is generalisable to the broad population undergoing surgery. It also contains numerous subgroup analyses which would allow it to be generalisable to specific patient groups.		
Applicability		
Included studies were performed in a wide range of countries. Eight of the 211 included studies were conducted in Australia. Given the wide range of included studies, the results are likely to be applicable to the Australian setting.		
Comments		

The authors conclude that antifibrinolytics provide worthwhile reductions in blood loss and transfusion requirements while not appearing to be offset by any serious safety issues. They also state that the lysine analogues appear to be generally as effective as aprotinin, but they are cheaper.

Abbreviations: CI, confidence interval; *het*, heterogeneity; ITT, intention to treat; MD, mean difference; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; WMD, weighted mean difference.

[a] Trials (N) in italics denotes the number of trials (N) included in the analysis. Trials in which the events occurred in 100% in both treatment arms, 0% in both treatment arms or in which a SD was not available were not estimable and were not included in the analysis.

STUDY DETAILS				
Citation				
DA Henry, PA Carless, D Fergusson, et al (2009) The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ 180(2): 183-193.				
Affiliation/Source of funds				
School of Medicine and Public Health, University of New castle, Newcastle, Australia; Ottawa Health Research Institute, The Ottawa Hospital, Ottawa, Canada; Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital; the Institute for Clinical Evaluative Sciences; Faculty of Medicine, University of Toronto, Toronto, Canada. Funding: No specific funding.				
Study design	Level of evidence	Location/setting		
Update of cardiac surgery subgroup from Henry 2007 Cochrane review (10 additional RCTs for aprotinin, 2 additional trials for tranexamic acid and 1 additional trial from ε-aminocaproic acid).	Level I	Hospital		
Intervention	Comparator			
Aprotinin, tranexamic acid, ε-aminocaproic acid	Placebo/no treatment or active			
Population characteristics				
Adults undergoing non-urgent cardiac surgery				
Length of follow-up	Outcomes measured			
Not specified	Myocardial infarction, mortality			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
All trials randomised. No further details for additional studies.	Comparison of baseline characteristics not assessed. Studies included and data extracted independently by at least two reviewers. Risk of bias assessed by two reviewers. (note: 16 trials not assessed for quality by both reviewers) Meta-analysis methods as per the Cochrane Collaboration.	Not reported for additional studies.	No evidence of publication bias for these outcomes. No evidence of treatment or measurement bias.	Not reported for additional studies.
Overall quality assessment (descriptive)				
Good. Comprehensive literature search carried out. Quality assessment undertaken. Some information missing for additional studies in publications, however the majority of the included studies were described in detail in the original Cochrane review (Henry 2007).				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)	
Aprotinin vs placebo/no treatment				

	n/N (%)	n/N (%)	
Incidence of blood transfusion 81 trials (N=9139) *NR*[a]	NR	NR	RR 0.66 (0.61, 0.72) P=NR (P*het*=NR)
Re-operation due to bleeding NR	NR	NR	RR 0.48 (0.34, 0.67) P=NR (P*het*=NR)
Myocardial infarction 42 trials (N=5884) *34 trials (N=5441)*	153/3329 (4.6)	115/2555 (4.5)	RR 0.94 (0.73, 1.21) P=NR (P*het*=NR)
Mortality 49 trials (N=7439) *32 trials (N=6279)*	101/4086 (2.5)	81/3353 (2.4)	RR 0.93 (0.69, 1.25) P=NR (P*het*=NR)
Tranexamic acid vs placebo/no treatment			
	n/N (%)	n/N (%)	
Incidence of blood transfusion NR	NR	NR	RR 0.70 (0.61, 0.80) P=NR (P*het*=NR)
Re-operation due to bleeding NR	NR	NR	RR 0.67 (0.41, 1.12) P=NR (P*het*=NR)
Myocardial infarction 16 trials (N=1732) *10 trials (N=1148)*	13/891 (1.5)	16/841 (1.9)	RR 0.86 (0.43, 1.75) P=NR (P*het*=NR)
Mortality 19 trials (N=1802) *11 trials (N=1390)*	8/922 (0.9)	16/880 (1.8)	RR 0.55 (0.24, 1.25) P=NR (P*het*=NR)
E-aminocaproic acid vs placebo/no treatment			
	n/N (%)	n/N (%)	
Incidence of blood transfusion NR	NR	NR	RR 0.75 (0.58, 0.96) P=NR (P*het*=NR)
Re-operation due to bleeding NR	NR	NR	RR 0.35 (0.11, 1.17) P=NR (P*het*=NR)
Myocardial infarction 5 trials (N=622)	12/340 (3.5)	14/322 (4.3)	RR 0.89 (0.37, 2.18) P=NR (P*het*=NR)
Mortality 5 trials (N=672)	7/346 (2.0)	3/326 (0.9)	RR 1.65 (0.50, 5.43) P=NR (P*het*=NR)

Outcome	Clinical importance	Clinical relevance
Aprotinin vs placebo		
Incidence of blood transfusion	1: Clinically important *benefit*, confidence limit does not include null value	1: Patient-relevant clinical outcome.
Re-operation due to	1: Clinically important *benefit*,	1: Patient-relevant clinical outcome.

bleeding	confidence limit does not include null value	
Myocardial infarction	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Mortality	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Tranexamic acid vs placebo		
Incidence of blood transfusion	1: Clinically important *benefit*, confidence limit does not include null value	1: Patient-relevant clinical outcome.
Re-operation due to bleeding	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Mortality	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
ε-aminocaproic acid vs placebo		
Incidence of blood transfusion	1: Clinically important *benefit*, confidence limit does not include null value	1: Patient-relevant clinical outcome.
Re-operation due to bleeding	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Mortality	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on patients who have undergone cardiac surgery so may only be generalisable to this group.		
Applicability		
Included studies were performed in a wide range of countries. Eight of the original 211 included studies were conducted in Australia. None of the 11 updated studies were conducted in Australia. Given the wide range of included studies, the results are likely to be applicable to the Australian setting.		
Comments		
The authors conclude that aprotinin has a higher risk of death than tranexamic acid and ε-aminocaproic acid, with no clear advantages. The risk of death for aprotinin compared with tranexamic acid in head-to-head trials was RR 1.43 (0.98, 2.08) while the risk of death for aprotinin compared with ε-aminocaproic acid in head-to-head trials was RR 1.49 (0.98, 2.28). These results are largely driven by the results of the large BART trial (Fergusson 2008).		

Abbreviations: CI, confidence interval; *het*, heterogeneity; ITT, intention to treat; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation.

[a] Trials (N) in italics denotes the number of trials (N) included in the analysis. Trials in which the events occurred in 100% in both treatment arms, 0% in both treatment arms or in which a SD was not available were not estimable and were not included in the analysis.

STUDY DETAILS				
Citation				
Kagoma YK, Crowther MA, Douketis J et al (2009) Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopaedic surgery: a systematic review of randomized trials. Thrombosis Research 123: 687-696.				
Affiliation/Source of funds				
Applied Science and Engineering, University of Toronto, Canada; Departments of Medicine and Hematology, McMaster University (St Josephs Hospital and Hamilton General Hospital), Hamilton, Canada; Department of Clinical Epidemiology and Biostatistics and Surgery (Division of Orthopedics), McMaster University, Hamilton, Canada. Funding not stated.				
Study design	Level of evidence	Location/setting		
Systematic review including 29 RCTs that investigated the effectiveness and safety of aprotinin (6 RCTs), tranexamic acid (19 RCTs) and ε-aminocaproic acid (1 RCT); also combination studies (3 RCTs) in patients undergoing total hip replacement or total knee arthroplasty.	Level I	Hospital		
Intervention	Comparator			
Aprotinin: all aprotinin dosages were a variation on the regimens recommended in the product monograph for CABG surgery. Tranexamic acid: Most doses were weight adjusted, ranging from 10-15 mg/kg. E-aminocaproic acid: doses ranged from 12.5 to 100 mg/kg, as well fixed doses of 5-10 g.	Placebo/no treatment			
Population characteristics				
Adult surgical patients undergoing total hip replacement or total knee arthroplasty.				
Length of follow-up	Outcomes measured			
3 days to 3 months	Blood loss; transfusion incidence; VTE.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all studies. Randomisation sequence described in 18 studies.	Baseline characteristics of intervention and control groups reported. Analysis of blood loss and VTE carried out using standardised mean difference (converted to RR for VTE).	20 studies double-blind.	Publication bias not assessed. Treatment or measurement bias not apparent.	No included studies reported ITT analysis. 4.1% of subjects excluded from analysis.
Overall quality assessment (descriptive)				
Good. The search strategy employed as well as study selection and extraction of data were adequate. Formal assessment of quality using Jadad Scale with 21/29 receiving a high rating.				
RESULTS				
Outcome No. trials (N) *No. trials included in analysis (N)*[a]	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)	
Aprotinin vs no aprotinin				
	Mean ± SD	Mean ± SD		

Total blood loss (mL) 6 trials (N=271)	NR	NR	WMD -639 (-725, -536) P<0.05 (P*het*=NR)
	n/N (%)	n/N (%)	
Transfusion incidence 5 trials (N=401)	NR	NR	RR 0.63 (0.50, 0.80) P<0.05 (P*het*=NR)
VTE 7 trials (N=481)	NR	NR	RD -0.04 (-0.09, 0.02) P>0.05 (Phet=NR)
Tranexamic acid vs no tranexamic acid			
	Mean ± SD	Mean ± SD	
Total blood loss (mL) 20 trials (N=1157)	NR	NR	WMD -393 (-442, -345) P<0.05 (P*het*=NR)
	n/N (%)	n/N (%)	
Transfusion incidence 21 trials (N=1237)	NR	NR	RR 0.47 (0.40, 0.55) P<0.05 (P*het*=NR)
VTE 21 trials (N=1237)	NR	NR	RD -0.01 (-0.04, 0.02) P>0.05 (Phet=NR)
E-aminocaproic acid vs ε-aminocaproic acid			
	Mean ± SD	Mean ± SD	
Total blood loss (mL) 2 trials (N=150)	NR	NR	WMD -331 (-544, -118) P<0.05 (P*het*=NR)
	n/N (%)	n/N (%)	
Transfusion incidence 3 trials (N=180)	NR	NR	RR 0.64 (0.21, 1.93) P≥0.05 (P*het*=NR)
VTE 3 trials (N=180)	NR	NR	RD 0.00 (-0.07, 0.07) P>0.05 (Phet=NR)

Outcome	Clinical importance	Clinical relevance
Aprotinin vs no aprotinin		
Blood loss	1: Clinically important *benefit*, confidence limit does not include null value (p<0.05).	1: Patient-relevant clinical outcome.
Transfusion incidence	1: Clinically important *benefit*, confidence limit does not include null value (p<0.05).	1: Patient-relevant clinical outcome.
VTE	4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Tranexamic acid vs no tranexamic acid		
Blood loss	1: Clinically important *benefit*, confidence limit does not include null value (p<0.05).	1: Patient-relevant clinical outcome.
Transfusion incidence	1: Clinically important *benefit*, confidence limit does not include null value (p<0.05).	1: Patient-relevant clinical outcome.
VTE	4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
E-aminocaproic acid vs ε-aminocaproic acid		
Blood loss	1: Clinically important *benefit*, confidence limit does not include null value (p<0.05).	1: Patient-relevant clinical outcome.
Transfusion incidence	4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
VTE	4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.

EXTERNAL VALIDITY
Generalisability
This systematic review focuses on adult patients who have undergone total hip replacement or total knee arthroplasty so may only be generalisable to these specific surgical populations. An analysis including all studies which separated out the two surgery types found the blood loss results were similar for each (WMD -1.12 ; 95% CI: -1.31, -0.93for THR and WMD -0.89; 95% CI: -1.05, -0.72 for TKA).
Applicability
This review does not report the locations of the included studies and as such the applicability of the results to the Australian/New Zealand setting is unclear.
Comments

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; *het*, heterogeneity; ITT, intention to treat; NR, not reported; RCT, randomised controlled trial; RD, risk difference; RR, relative risk; SD, standard deviation; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism; WMD, weighted mean difference.

[a] Where individual studies had either 100% events in both treatment arms, no events in both treatment arms or no SD was reported, a risk estimate for that individual study could not be calculated, and it could not be included in the pooled analysis. Where this has occurred, the actual number of studies and subjects included in the analysis will be stated.

STUDY DETAILS				
Citation				
Systematic review: Kongnyuy EJ, Wiysonge CS (2009) Interventions to reduce haemorrhage during myomectomy for fibroids. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD005335. DOI: 10.1002/14651858.CD005335.pub3. *Single included RCT:* Caglar GS, Tasci Y, Kayikcioglu F et al (2008) Intravenous tranexamic acid use in myomectomy: a prospective randomised double-blind placebo controlled study. European Journal of Obstetrics, Gynecology and Reproductive Biology 137(): 227-231.				
Affiliation/Source of funds				
Systematic review: Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Liverpool, UK; Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa. Funding: Saltonstall Fund for Pain Research, USA. *Single included RCT:* Ankara Etlick Maternity and Women's Health Teaching Research Hospital, Ankara, Turkey. Funding: not stated.				
Study design	Level of evidence		Location/setting	
Systematic review including 10 RCTs that assessed the effectiveness and safety of intervention to reduce haemorrhage during myomectomy for fibroids. Only 1 of the 10 included RCTs related to TXA.[a]	Level II		Hospital	
Intervention		Comparator		
TXA: bolus injection of 10 mg/kg (max 1 g) 15 minutes before incision followed by a continuous infusion of mg/kg/hr dissolved in 1 L saline for 10 h (max 1 g/10 hr).		Placebo: saline (same regimen as TXA)		
Population characteristics				
Women scheduled for myomectomy due to myoma uteri. Mean age 35 years, volume of myomas 457 cm^3 ± SD 669 in the intervention group and 286 cm^3 ± SD 259 in the control group. Authors state no difference in any baseline characteristics or number and volume of myomas between groups.				
Length of follow-up		Outcomes measured		
In hospital		Blood loss; duration of surgery, haemoglobin, haematocrit, blood transfusion requirements on ward.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Patients randomised according to a computer-generate sequence. Allocation by sequentially numbered drug containers of identical appearance.	Authors state no difference in any baseline characteristics or number and volume of myomas between groups. Analysis not described.	Double-blind. Patients, surgeons and anaesthetists unaware of treatment assignment.	No suggestions of selective reporting. Unclear whether there are other sources of bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
RCT: Good. Systematic review: Good. Extensive literature search, data assessed for quality.				
RESULTS				

Outcome No. trials (N) *No. trials included in analysis (N)*[a]	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)
Tranexamic acid vs placebo			
	N=50	N=50	Risk estimate (95% CI) P value
	n/N (%)	n/N (%)	
Transfusion incidence	15/50 (30)	10/50 (20)	OR 1.71 (0.68, 4.30) P=0.25
	Mean ± SD	Mean ± SD	
Blood loss (mL)	804 ± 482	1047 ± 617	MD -243.00 (-460.02, -25.98) P=0.028
Postoperative haemoglobin (g/dL)	9.97 ± 1.5	9.76 ± 1.4	MD 0.21 (-0.36, 0.78) P=0.47

Outcome	Clinical importance	Clinical relevance
Tranexamic acid vs placebo		
Transfusion incidence	4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
Blood loss	1: Clinically important *benefit*, confidence limit does not include null value (p=0.028).	1: Patient-relevant clinical outcome.
Postoperative haemoglobin	4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on adult female patients undergoing myomectomy for uterine fibroids and only includes one relevant RCT for this intervention. Therefore, it is likely to only be generalisable to this select patient group.		
Applicability		
The included RCT was conducted at a single centre in Turkey so may not be directly applicable to the Australian/New Zealand setting.		
Comments		

Abbreviations: CI, confidence interval; het, heterogeneity; ITT, intention to treat; MD, mean difference; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

[a] Where individual studies had either 100% events in both treatment arms, no events in both treatment arms or no SD was reported, a risk estimate for that individual study could not be calculated, and it could not be included in the pooled analysis. Where this has occurred, the actual number of studies and subjects included in the analysis will be stated.

[a] All information relating to the single included RCT was taken from information provided in the Kongnyuy 2009 systematic review.

STUDY DETAILS				
Citation				
Liu C-M, Chen J, Wang X-H (2008) Requirements for liver transfusion and postoperative outcomes in orthotopic liver transplantation: a meta-analysis on aprotinin. World J Gatroenterol 14(9): 1425-1429.				
Affiliation/Source of funds				
Departments of Surgery and Hepatobiliary Surgery, First Affiliated Hospital of Nanjing Medical University, Nanjing, China. Funding: Supported by Grant 02KJD320015 from the Education Committee of Jiangsu province, China.				
Study design	Level of evidence	Location/setting		
Systematic review including 6 RCTs and 1 non-RCT that assessed the effectiveness and safety of aprotinin in liver transplantation. One study included tranexamic acid as a control and has been excluded from the analyses presented here.	Level I	Hospital		
Intervention	Comparator			
Aprotinin: various doses use, not stated.	Placebo/no treatment			
Population characteristics				
Adult patients undergoing orthotopic liver transplantation; no further details of patients provided.				
Length of follow-up	Outcomes measured			
Not stated	Thrombotic events (this is the only outcome included here as it included data from RCTs only)			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomisation in RCTs not described. 1 included study non-randomised	No details on comparison of baseline characteristics. Analyses conducted using RevMan.	Blinding status of studies not reported.	Unclear	Unclear
Overall quality assessment (descriptive)				
Poor. Little information on included studies. One included study was a non-randomised controlled trial. This study had more highly beneficial results compared to the other studies for transfusion volume and had greater mortality and less reoperation for bleeding than the other studies. Also, one RCT compared aprotinin with tranexamic acid. For this reason, this study was included only for the thrombosis outcome which was based on data from 2 placebo-controlled RCTs.				
RESULTS				
Outcome No. trials (N) *No. trials included in analysis (N)*[a]	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI)	
Aprotinin vs placebo[a]				
	Mean ± SD	Mean ± SD		
	n/N (%)	n/N (%)	Risk estimate (95% CI)	
Thromboembolic events 2 RCTs (N=200)	3/122 (2.5)	5/78 (6.4)	OR 0.38 (0.09, 1.64) P>0.05 (P*het*=0.88)	
Outcome	Clinical importance	Clinical relevance		
Aprotinin vs placebo				
Thromboembolic events	4: Range of estimates includes clinically important effects, but also compatible with no effect	1: Patient-relevant clinical outcome.		
EXTERNAL VALIDITY				
Generalisability				
This systematic review focuses on adult patients undergoing orthotopic liver transplantation. It is likely to only be generalisable to this select patient group.				

Applicability
There is no information provided at to the locations of the included studies so it is not possible to determine whether the results would be directly applicable to the Australian/New Zealand setting.
Comments

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma; het, heterogeneity; ITT, intention to treat; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; WMD, weighted mean difference.

[a] Where individual studies had either 100% events in both treatment arms, no events in both treatment arms or no SD was reported, a risk estimate for that individual study could not be calculated, and it could not be included in the pooled analysis. Where this has occurred, the actual number of studies and subjects included in the analysis will be stated.

[a] Only the analysis excluding the RCT comparing aprotinin with tranexamic acid is presented here.

STUDY DETAILS				
Citation				
DR McIlroy, PS Myles, LE Phillips, JA Smith Antifibrinolytics in cardiac surgical patients receiving aspirin: a systematic review and meta-analysis				
Affiliation/Source of funds				
Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Melbourne, Australia; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; Department of Surgery, Monash Medical Centre, Melbourne, Australia. Funding: Alfred Hospital anaesthesia research fund.				
Study design	Level of evidence	Location/setting		
Systematic review including 17 RCTs that investigated the effects of aprotinin, tranexamic acid and ε-aminocaproic acid on blood loss and use of blood products in cardiac surgery patients receiving aspirin.	Level I	Hospital		
Intervention	Comparator			
Aprotinin, tranexamic acid or ε-aminocaproic acid	Placebo, no treatment or active			
Population characteristics				
Adult patients undergoing CABG ± valve surgery where aspirin had been maintained or initiated through the prospective period.				
Length of follow-up	Outcomes measured			
Not specified	Blood loss (chest tube drainage); incidence of transfusion; re-operation; thrombotic complication;			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all 17 studies except one which was pseudo-randomised. Method adequate for 5 trials, inadequate in 1 trial and unclear in the remaining trials.	Baseline characteristics of intervention and control groups not reported. Methodological quality of studies assessed independently by two authors. Disagreements resolved by consensus. Random effects model used for all analyses. Heterogeneity assessed.	12 trials double-blind, 4 open-label.	No evidence of publication bias found.	No studies judged to be at high risk of attrition bias, 4 judged to be at moderate risk, 7 judged to be at low risk. Remaining studies unable to judge.
Overall quality assessment (descriptive)				
Good. Comprehensive literature search carried out. Quality assessment undertaken. Appropriate analysis methods used. Subgroup and sensitivity analyses undertaken.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Aprotinin vs placebo				
Blood loss (postoperative chest tube loss) mL 12 trials (N=992)	NR	NR	WMD -432.51 (-543.68, -321.35) P<0.001 (P*het*<0.001)	
Incidence of transfusion 10 trials (N=856)	205/510 (40.2)	229/346 (66.2)	OR 0.34 (0.25, 0.46) P<0.001 (P*het*=0.75)	

Re-operation 7 trials (N=352) *4 trials (N=198)*[a]	5/186 (2.7)	10/166 (6.0)	OR 0.42 (0.13, 1.36) P=0.15 (P*het*=0.61)
Thrombotic complication 8 trials (N=527) *3 trials (N=174)*	10/269 (3.7)	17/258 (6.6)	OR 0.51 (0.21, 1.20) P=0.12 (P*het*=0.76)
Lysine analogue (tranexamic acid or ε-aminocaproic acid) vs placebo			
Blood loss (postoperative chest tube loss) mL 3 trials (N=259)	NR	NR	WMD -189.35 (-287.24, -91.46) P<0.001 (P*het*=0.05)
Incidence of transfusion 1 trial (N=79)	8/40 (20.0)	8/39 (20.5)	OR 0.97 (0.32, 2.90) P=0.95 (P*het*=NA)
Re-operation 2 trials (N=109)	0/55 (0.0)	2/54 (3.7)	OR 0.31 (0.03, 3.14) P=0.32 (P*het*=0.99)
Thrombotic complication 3 trials (N=259) *1 trial (N=79)*	0/155 (0.0)	1/104 (1.0)	OR 0.32 (0.01, 8.02) P=0.49 (P*het*=NA)

Outcome	Clinical importance	Clinical relevance
Aprotinin vs placebo		
Blood loss	1: Clinically important benefit, confidence limit does not include null value (P<0.001)	1: Patient-relevant clinical outcome.
Incidence of transfusion	1: Clinically important benefit, confidence limit does not include null value (P<0.001)	1: Patient-relevant clinical outcome.
Re-operation	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Thrombotic complication	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Lysine analogue vs placebo		
Blood loss	1: Clinically important benefit, confidence limit does not include null value (P<0.001)	1: Patient-relevant clinical outcome.
Incidence of transfusion	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Re-operation	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Thrombotic complication	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.

EXTERNAL VALIDITY
Generalisability
This systematic review focuses on cardiac surgical patients who are also receiving aspirin. Therefore, the results of this review are likely to be generalisable only to this specific population.
Applicability
The locations of the included studies are not reported so it is not possible to comment on the applicability to the Australian setting.

Comments
The authors concluded that antifibrinolytics were effective at reducing blood loss and transfusion requirements in cardiac surgery patients using aspirin.

Abbreviations: CABG, coronary artery bypass graft; *het*, heterogeneity; ITT, intention to treat; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; SD, standard deviation; WMD, weighted mean difference.

[a] Trials (N) in italics denotes the number of trials (N) included in the analysis. Trials in which the events occurred in 100% in both treatment arms, 0% in both treatment arms or in which a SD was not available were not estimable and were not included in the analysis.

STUDY DETAILS				
Citation				
ES Schouten, AC van de Pol, ANJ Schouten et al The effect of aprotinin, tranexamic acid and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis.				
Affiliation/Source of funds				
Division of Pediatric Intensive care and Division of Perioperative Care4 and Emergency Medicine, Wilhelmina Children's Hospital, University Medical Canter, Utrecht, The Netherlands				
Study design	Level of evidence	Location/setting		
Systematic review including 28 RCTs that investigated the effects of aprotinin, tranexamic acid and ε-aminocaproic acid on blood loss and use of blood products	Level I	Hospital		
Intervention	Comparator			
Aprotinin, tranexamic acid or ε-aminocaproic acid	Placebo or no treatment			
Population characteristics				
Children undergoing cardiac or scoliosis surgery				
Length of follow-up	Outcomes measured			
Not specified	Blood loss; transfusion (PRC, plasma or thrombo)			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all 28 studies. Method of randomisation not described. Only 3/28 studies scored 2/2 for allocation, the remaining studies scored 1.	Baseline characteristics of intervention and control groups not reported. Methodological quality of studies assessed independently by two authors. Disagreements resolved by discussion. Model used not stated. Studies considered too heterogeneous for pooling if I2 statistic ≥ 50%.	11/28 studies double-blind, 13/28 studies single-blind, and remaining studies not blinded.	Publication bias assessed. No evidence of treatment/measurement bias.	16/28 studies had good (> 80%) follow-up, 5/28 studies had moderate follow-up (50-80%) and the remaining studies had poor follow-up.
Overall quality assessment (descriptive)				
Good. Comprehensive literature search carried out. Quality assessment undertaken. Meta-regression analysis carried out to identify potential confounders for the cardiac studies due to heterogeneity (age, weight and time on cardiopulmonary bypass).				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Aprotinin vs placebo				
Blood loss				
	Mean ± SD	Mean ± SD		
14 trials (N=594)	NR	NR	*Cardiac surgery* NR due to heterogeneity	
1 trial (N=44)	NR	NR	Scoliosis surgery WMD -385 mL (-727, -42) P=NR (I^2=NA)	
Transfusion (packed red cells)				
	Mean ± SD	Mean ± SD		

3 trials (N=250)	NR	NR	*Cardiac surgery* WMD -4 mL/kg (-7, -2) P=NR (I^2=0%)
Transfusion (plasma)			
	Mean ± SD	Mean ± SD	
2 trials (N=228)	NR	NR	*Cardiac surgery* WMD -5 mL/kg (-8, -2) P=NR (I^2=0%)
Transfusion (thrombo)			
	Mean ± SD	Mean ± SD	
NR (N=180)	NR	NR	*Cardiac surgery* NR due to heterogeneity
Tranexamic acid vs placebo			
Blood loss			
	Mean ± SD	Mean ± SD	
6 trials (N=542)	NR	NR	*Cardiac surgery* WMD -11 mL/kg (-13, -8) P=NR (I^2=31%)
2 trials (N=84)	NR	NR	*Scoliosis surgery* WMD -682 mL (-1149, -214) P=NR (I^2=24%)
Transfusion (packed red cells)			
	Mean ± SD	Mean ± SD	
5 trials (N=460)	NR	NR	*Cardiac surgery* WMD -7 mL/kg (-10, -5) P=NR (I^2=6%)
2 trials (N=84)	NR	NR	*Scoliosis surgery* WMD -349 mL (-620, -77) P=NR (I^2=0%)
Transfusion (plasma)			
	Mean ± SD	Mean ± SD	
4 trials (N=419)	NR	NR	*Cardiac surgery* WMD -7 mL/kg (-9, -4) P=NR (I^2=0%)
2 trials (N=84)	NR	NR	*Scoliosis surgery* WMD -15 mL (-127, 98) P=NR (I^2=24%)
Transfusion (thrombo)			
	Mean ± SD	Mean ± SD	
NR (N=370)	NR	NR	*Cardiac surgery* WMD -5 mL/kg (-7, -3) P=NR (I^2=0%)
E-aminocaproic acid vs placebo			
Blood loss			
	Mean ± SD	Mean ± SD	
3 trials (N=410)	NR	NR	*Cardiac surgery* NR due to heterogeneity
1 trial (N=36)	NR	NR	*Scoliosis surgery* WMD -59 mL (-262, 144) P=NR (I^2=NA)
Transfusion (packed red cells)			
	Mean ± SD	Mean ± SD	
3 trials (N=410)	NR	NR	*Cardiac surgery* NR due to heterogeneity
Transfusion (plasma)			
	Mean ± SD	Mean ± SD	

3 trials (N=410)	NR	NR	*Cardiac surgery* WMD -3 mL/kg (-5, -1) P=NR (I^2=20%)
Transfusion (thrombo)			
	Mean ± SD	Mean ± SD	
3 trials (N=410)	NR	NR	*Cardiac surgery* NR due to heterogeneity

Outcome	Clinical importance	Clinical relevance
Aprotinin vs placebo		
Blood loss	*Scoliosis surgery* 1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Transfusion (packed red cell)	*Cardiac surgery* 1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Transfusion (plasma)	*Cardiac surgery* 1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Tranexamic acid vs placebo		
Blood loss	*Cardiac surgery* 1: Clinically important benefit, confidence limit does not include null value. *Scoliosis surgery* 1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Transfusion (packed red cell)	*Cardiac surgery* 1: Clinically important benefit, confidence limit does not include null value. *Scoliosis surgery* 1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
Transfusion (plasma)	*Cardiac surgery* 1: Clinically important benefit, confidence limit does not include null value. *Scoliosis surgery* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Transfusion (thrombo)	*Cardiac surgery* 1: Clinically important benefit, confidence limit does not include null value.	
Tranexamic acid vs placebo		

Blood loss	*Scoliosis surgery* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Transfusion (plasma)	*Cardiac surgery* 1: Clinically important benefit, confidence limit does not include null value.	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on paediatric patients (<18 years) undergoing cardiac or scoliosis surgery. Therefore, the results of this review are likely to be generalisable only to this specific population.		
Applicability		
The locations of the included studies are not reported so it is not possible to comment on the applicability to the Australian setting.		
Comments		
The authors concluded that there was no evidence than tranexamic acid and ε-aminocaproic acid are less effective than aprotinin in major paediatric surgery.		

Abbreviations: ITT, intention to treat; NA, not applicable; NR, not reported; PRC, packed red cell; RCT, randomised controlled trial; SD, standard deviation; WMD, weighted mean difference.

STUDY DETAILS				
Citation				
Tzortzopoulou A, Cepeda MS, Schumann R et al (2008) Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD006883. DOI: 10.1002/14651858.pub2.				
Affiliation/Source of funds				
Department of Anesthesia, Tufts medical Center, Boston, US; Pharmacoepidemiology, Johnson & Johnson Pharmaceutical Research and development, Titussville, US. Funding: Saltonstall Fund for pain Research, US.				
Study design	Level of evidence	Location/setting		
Systematic review including 6 RCTs that investigated the effects of aprotinin (2 RCTs), tranexamic acid (2 RCTs) and ε-aminocaproic acid (2 RCTs) on blood loss and transfusion in children undergoing surgery for primary or secondary scoliosis.	Level I	Hospital		
Intervention	Comparator			
Aprotinin: High-dose regimen Tranexamic acid: 1 high-dose regimen and 1 low-dose regimen E-aminocaproic acid: high-dose regimen	Placebo			
Population characteristics				
Children (< 18 years) undergoing primary or secondary scoliosis surgery. Mean age 14.1 years (idiopathic scoliosis) and 13.2 years (idiopathic and secondary scoliosis); 72.5% female (idiopathic scoliosis) and 44.1% female (idiopathic and secondary scoliosis).				
Length of follow-up	Outcomes measured			
In-hospital	Blood loss, transfusion incidence, transfusion volume, mortality, morbidity.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised allocation was reported in all 6 studies; described in 5 studies (1 computer-generated, 2 random number tables, 2 drawing numbers from container).	Methodological quality of studies assessed independently by two authors. Disagreements resolved by discussion. 4/6 studies rated A (low risk o bias) and 2/6 rated B (moderate risk of bias).	5/6 studies double-blind. 1 study not described.	No evidence of treatment/measurement bias.	All studies described as having in ITT analysis.
Overall quality assessment (descriptive)				
Good. Comprehensive literature search carried out. Quality assessment undertaken. Studies rated as having low-moderate risk of bias.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance Risk estimate (95% CI) P value (*heterogeneity*)	
Aprotinin vs placebo				
Transfusion incidence				
	n/N (%)	n/N (%)		

1 RCT (N=43)	8/15 (53.3)	20/28 (71.4)	RR 0.75 (0.44, 1.27) P=0.28 (P*het*=NA)
Transfusion volume (mL)			
	Mean ± SD	Mean ± SD	
2 RCTs (N=87)	NR	NR	WMD -361.42 (-583.88, -138.96) P=0.0015 (P*het*=0.80)
Blood loss (mL)			
	Mean ± SD	Mean ± SD	
2 RCTs (N=87)	NR	NR	WMD -450.32 (-726.35, -174.29) P=0.0014 (P*het*=0.53)
Mortality			
	n/N (%)	n/N (%)	
2 RCTs (N=87)	0/15 (0)	0/28 (0)	NA
Renal insufficiency			
	n/N (%)	n/N (%)	
2 RCTs (N=87)	0/15 (0)	0/28 (0)	NA
Tranexamic acid vs placebo			
Transfusion incidence			
	n/N (%)	n/N (%)	
2 RCTs (N=84)	20/45 (44.4)	21/39 (53.8)	RR 0.84 (0.56, 1.27) P=0.41 (P*het*=0.94)
Transfusion volume (mL)			
	Mean ± SD	Mean ± SD	
2 RCTs (N=84)	NR	NR	WMD -395.14 (-687.55, -102.73) P=0.0081 (P*het*=0.51)
Blood loss (mL)			
	Mean ± SD	Mean ± SD	
2 RCTs (N=84)	NR	NR	WMD -681.81 (-1149.12, -214.49) P=0.0042 (P*het*=0.25)
Mortality			
	n/N (%)	n/N (%)	
2 RCTs (N=84)	0/45 (0)	0/39 (0)	NA
Renal insufficiency			
	n/N (%)	n/N (%)	
2 RCTs (N=84)	0/45 (0)	0/39 (0)	NA
E-aminocaproic acid vs placebo			
Transfusion incidence			
	n/N (%)	n/N (%)	
1 RCT (N=36)	14/19 (73.7)	12/17 (70.6)	RR 1.04 (0.69, 1.57) P=0.84 (P*het*=NA)
Transfusion volume (mL)			
	Mean ± SD	Mean ± SD	
1 RCT (N=84)	NR	NR	WMD -245.00 (-481.03, -8.97) P=0.042 (P*het*=NA)
Blood loss (mL)			
	Mean ± SD	Mean ± SD	
1 RCT (N=36)	NR	NR	WMD -325.00 (-586.83, -63.17) P=0.015 (P*het*=NA)
Mortality			
	n/N (%)	n/N (%)	

2 RCTs (N=83)	0/46 (0)	0/37 (0)	NA
Renal insufficiency			
	n/N (%)	n/N (%)	
1 RCTs (N=36)	0/19 (0)	0/17 (0)	NA
DVT			
	n/N (%)	n/N (%)	
1 RCTs (N=47)	0/27 (0)	3/20 (15)	Not estimable P=0.07

Outcome	Clinical importance	Clinical relevance
Aprotinin vs placebo		
Transfusion incidence	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Transfusion volume	1: Clinically important benefit, confidence limit does not include null value (p=0.0015).	1: Patient-relevant clinical outcome.
Blood loss	1: Clinically important benefit, confidence limit does not include null value (p=0.0014).	1: Patient-relevant clinical outcome.
Mortality	There were no deaths in either treatment arm.	1: Patient-relevant clinical outcome.
Renal insufficiency	There were no cases of renal insufficiency in either treatment arm	1: Patient-relevant clinical outcome.
Tranexamic acid vs placebo		
Transfusion incidence	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Transfusion volume	1: Clinically important benefit, confidence limit does not include null value (p=0.0081).	1: Patient-relevant clinical outcome.
Blood loss	1: Clinically important benefit, confidence limit does not include null value (p=0.0042).	1: Patient-relevant clinical outcome.
Mortality	There were no deaths in either treatment arm.	1: Patient-relevant clinical outcome.
Renal insufficiency	There were no cases of renal insufficiency in either treatment arm	1: Patient-relevant clinical outcome.
E-aminocaproic acid vs placebo		
Transfusion incidence	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Transfusion volume	1: Clinically important benefit, confidence limit does not include null value (p=0.042).	1: Patient-relevant clinical outcome.
Blood loss	1: Clinically important benefit, confidence limit does not include null value (p=0.015).	1: Patient-relevant clinical outcome.
Mortality	There were no deaths in either treatment arm.	1: Patient-relevant clinical outcome.
Renal insufficiency	There were no cases of renal insufficiency in either treatment arm	1: Patient-relevant clinical outcome.

DVT	4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect (p=0.07)	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
This systematic review focuses on paediatric patients (<18 years) undergoing surgery for primary or secondary scoliosis. Therefore, the results of this review are likely to be generalisable only to this specific population.		
Applicability		
The locations of the included studies are not reported so it is not possible to comment on the applicability to the Australian/New Zealand setting.		
Comments		

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; *het*, heterogeneity; ITT, intention to treat; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; WMD, weighted mean difference.

Level II evidence

STUDY DETAILS				
Citation				
Alvarez JC, Santiveri FX, Ramos I et al (2008) Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. Transfusion 48: 519-525.				
Affiliation/Source of funds				
Department of Anesthesiology and the Department of Orthopedic Surgery, University Hospital of Mar, Barcelona, Spain No details of funding reported.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital (single-centre)	
Intervention		Comparator		
Tranexamic acid: a bolus of 10 mg/kg administered by the research anaesthetist 30 minutes before deflation of the tourniquet followed by an infusion of 1 mg/kg/hr starting at the end of the operation and continuing during the first 6 postoperative hours		Placebo: regimen as per tranexamic acid		
Population characteristics				
ASA-I to III[a] patients diagnosed with osteoarthritis and undergoing unilateral bicondylar cemental total knee arthroplasty. Mean age 72; female 82%; BMI 31.				
Length of follow-up		Outcomes measured		
Up to 3 months postoperative (for thrombosis)		Primary outcome: transfusion rate Secondary outcome: postoperative blood loss Safety outcome: thrombosis		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Computer-generated random numbers/sealed envelopes. Treatment prepared by an anaesthetist not otherwise engaged in the study.	Results determined by anaesthetist not aware of treatment assignment. .	Double-blind. Neither patient not the anaesthetist assessing results aware of treatment assignment.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	15 subjects excluded from analysis following randomisation (9 in treatment group and 6 in control group) due to release of tourniquet (7), no epidural catheter (7) and error during blood sampling (1)
Overall quality assessment (descriptive)				
Fair. 15 subjects excluded from analysis post-randomisation (9 in treatment group and 6 in control group). These subjects were not further described. The authors note this is a limitation of the study.				
RESULTS				
Outcome	Intervention group N=46	Comparator group N=49	Statistical significance	
Tranexamic acid				
	n/N (%)	n/N (%)	P value	
Transfusion incidence (allogeneic and autologous blood)	1/46 (2.2)	6/49 (12.2)	0.06 *(post-hoc)*	
Transfusion incidence (recovered blood)	2/46 (4.3)	36/49 (73.5)	<0.0001	
	Mean ± SD	Mean ± SD	P value	
Total RBC transfusion in transfused patients only (units)	1 (1 unit in 1 patient)	1.8 (11 units in 6 patients)	NR	

Allogeneic RBC transfusion in transfused patients only (units)	1 (1 unit in 1 patient)	NR (8 unit; number of patients NR)	NR
Autologous RBC transfusion in transfused patients only (units)	0	NR (3 unit; number of patients NR)	NR
Chest tube blood loss at 0-6 hr postoperative (mL)	159 ± 110	534 ± 351	<0.0001
Chest tube blood loss at 6 hr - 4 day postoperative (mL)	132 ± 151	132 ± 150	0.98
Total chest tube blood loss (mL)	170 ± 109	551 ± 352	<0.001
	n/N (%)	n/N (%)	P value
Thrombosis	0/46 (0)	0/49 (0)	NA
1. Haemoglobin			
	Mean ± SD	Mean ± SD	P value
Haemoglobin (preoperative)	13.5	13.6	NS
Haemoglobin (end of surgery)	11.9	11.9	NS
Haemoglobin (6 hr postoperative)	11.5	10.9	P<0.05
Haemoglobin (4 day postoperative)	10.4	9.9	P<0.05

Clinical importance		Clinical relevance
Tranexamic acid		
Transfusion incidence	*Allogeneic and autologous blood* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Recovered blood* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.
Transfusion volume	*Total RBC transfusion in transfused patients* Unclear. No formal statistical comparison made. *Allogeneic RBC transfusion* Unclear. No formal statistical comparison made. *Autologous RBC transfusion* Unclear. No formal statistical comparison made.	1: Patient-relevant clinical outcome.
Blood loss	*Chest-tube blood loss (0-6 hr)* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Chest-tube blood loss (6 hr – 4 day)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Chest-tube blood loss (total)* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.
Morbidity	*Thrombosis* No events in either group	1: Patient-relevant clinical outcome.

Haemoglobin	*End of surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *6 hr postoperative* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05) *4 day postoperative* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05)	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in total knee arthroplasty in patients with ASA-I – III so likely to only be generalisable to this select population. The authors note the dosing in this study is lower that seen is other studies and so results may not be generalisable to higher doses of tranexamic acid.		
Applicability		
Study conducted in a single centre in Spain so may not be completely applicable to the Australian/New Zealand setting.		
Comments		
33 patients underwent preoperative blood conservation programme (includes autologous blood transfusion, treatment with rHuEPO, and administration of elemental iron). The authors state there was no difference between groups regarding the use of these treatments. The authors note that the study was not sufficiently powered to show a difference between tranexamic acid and placebo with regards to thrombosis.		

Note: All post-hoc calculations performed using GraphPad software.

Abbreviations: ASA, American Society of Anaesthesiologist; BMI, body mass index; ITT, intention-to-treat; NA, not applicable, NR, not reported; NS, not significant; RBC, red blood cell; RCT, randomised controlled trial; rHuEPO, recombinant human erythropoietin; SD, standard deviation.

[a] A system used by anaesthesiologists to stratify severity of patients' underlying disease and potential for suffering complications from general anaesthesia . American Society of Anesthesiology (ASA) patient classification status defined as follows: ASA I – normal healthy patient; ASA II – patient with mild systemic disease; no functional limitation; ASA III – patient with severe systemic disease; definite functional impairment; ASA IV – patient with severe systemic disease that is a constant threat to life; ASA V – unstable moribund patient who is not expected to survive 24 hours with or without the operation; ASA VI –brain-dead patient whose organs are removed for donation to another ; E – emergency operation of any type, which is added to any of the 6 above categories.

STUDY DETAILS				
Citation				
Apostolakis E, Panagopoulos N, Koletsis EN, Crockett J, Stamou-Kouki H, Sourgiadaki E, Filos K, Dougenis D (2008) Influence of ultra low dose aprotinin on thoracic surgical operations: a prospective randomized trial. Journal of Cardiothoracic Surgery 3:14.				
Affiliation/Source of funds				
Departments of Cardiothoracic Surgery and Anesthesiology, Patras University School of Medicine, Patras, Greece.				
Study design	Level of evidence		Location/setting	
Single-blind RCT	II		Hospital (single-centre)	
Intervention		Comparator		
Ultra-low dose aprotinin: test dose of 1mL following intubation; 500,000 IU IV in 50 mL over 15 mins; same dose following closure.		Placebo: 0.9% saline (regimen as per aprotinin)		
Population characteristics				
Adult patients undergoing major thoracic surgery. Mean age 58 years; female 10%, BMI ~ 25 kg/m^2.				
Length of follow-up		Outcomes measured		
Hospitalisation period		Blood loss, transfusion requirements, postoperative complications.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised using randomisation tables.	Standard statistical methods used.	Single-blind. Anaesthetist aware of treatment allocation. Surgeons unaware until patients transferred to ward.	Staff measuring outcomes blinded to treatment allocation so not likely to be treatment or measurement bias. Possible potential for bias due to anaesthetist knowing allocation.	All patients included in analysis.
Overall quality assessment (descriptive)				
Fair. Random treatment allocation, treating anaesthetist aware of assignment so possibility of bias; small trial.				
RESULTS				
Outcome	Intervention group N=29	Placebo N=30	Statistical significance	
Ultra-low dose aprotinin (IV)				
	Mean ± SD	Mean ± SD	P value	
Intraoperative pRBCs transfused (units)	0.17 ± 0.539	0.17 ± 0.531	0.967	
Postoperative pRBCs transfused (units)	0.00 ± 0.00	0.03 ± 0.183	0.97	
Intraoperative FFP transfused (units)	0.21 ± 0.620	0.20 ± 0.761	0.330	
Postoperative FFP transfused (units)	0.21 ± 0.620	0.87 ± 1.525	0.035	
Day 1 postoperative thoracic drainage (mL)	412.6 ± 199.2	764.3 ± 213.9	<0.001	
Day 2 postoperative thoracic drainage (mL)	248.3 ± 178.5	455.0 ± 274.6	0.001	
In-hospital mortality	0/29 (0)	0/30 (0)	NA	
Re-operation for bleeding	0/29 (0)	0/30 (0)	NA	
Clinical importance		Clinical relevance		
Ultra-low-dose aprotinin (IV)				

Transfusion volume	*Intraoperative pRBCs* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative pRBCs* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative FFP* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative FFP* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.035)	1: Patient-relevant clinical outcome.
Blood loss	*Day 1 postoperative thoracic drainage* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Day 2 postoperative thoracic drainage* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001)	1: Patient-relevant clinical outcome.
Mortality	*In hospital mortality* There were no deaths in either treatment arm	1: Patient-relevant clinical outcome.
Reoperation for bleeding	*In hospital mortality* There was no reoperation due to bleeding in either treatment arm	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing thoracic surgery (or which most received a lateral thoracotomy for lung resection) so likely to only be generalisable to this select surgical population.		
Applicability		
Study conducted in a single centre in Greece so may possibly be applicable to the Australian/New Zealand setting.		
Comments		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS				
Citation				
Athanasiadis T, Beule AG, Wormald PJ (2007) Effects of topical antifibrinolytics in endoscopic sinus surgery: a pilot randomized controlled trial. Am J Rhinol 21: 737-742.				
Affiliation/Source of funds				
Department of Otorhinolaryngology, Head and Neck Surgery, The Queen Elizabeth Hospital, University of Adelaide, Australia; Department of Otorhinolaryngology, Head and Neck Surgery, University of Greifswald, Greifswald, Germany.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital	
Intervention	Comparator			
Topical ε-aminocaproic acid 2.5 g; topical tranexamic acid 100 mg; topical tranexamic acid 1g	Placebo (saline) – used in contralateral side.			
Population characteristics				
Aged > 18 years; undergoing bilateral endoscopic sinus surgery (ESS) involving complete sphenoethmoidectomy and frontal recess clearance for chronic sinusitis; 63% male; median age 51 years (19-79).				
Length of follow-up	Outcomes measured			
Efficacy measured for up to 10 minutes. Blood samples for safety analysis taken 6 hours after application of treatment.	Scoring system based on bleeding (Wormald grading scale and Boezaart grading scale) measured at 0, 2, 4, 6, 8 and 10 mins following application of treatment. Postoperative adverse events. Postoperative coagulation parameters.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised to treatment and placebo (ie, left or right side). Method of randomisation not reported.	Grading performed by surgeon and independent observer.	Double-blind. Surgical team and independent observer blinded to treatment allocation. Treatments prepared by anaesthetist and given to nurse – labelled left and right for left and right sinus.	Surgeon and observer blinded to treatment allocation so not likely to be treatment or measurement bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Fair. Method used to randomise not stated and anaesthetist prepared treatment so potential for unbinding. Use of rating scales that have not been validated.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
E-aminocaproic acid 2.5 g				
Wormald grading scale	No difference between ACA and placebo		NR	
Boezaart grading scale	No difference between ACA and placebo		NR	
Epistaxis	No difference between ACA and placebo		NR	
Tranexamic acid 100 mg				
Wormald grading scale	Significant difference between TA and placebo at 2 mins, 4 mins and 6 mins		P<0.05	
Boezaart grading scale	Significant difference between TA and placebo at 2 mins, 4 mins and 6 mins		P<0.05	
Epistaxis	No difference between TA and placebo		NR	
Tranexamic acid 1 g				
Wormald grading scale	No significant difference between TA and placebo		P>0.05	
Boezaart grading scale	No significant difference between TA and placebo		P>0.05	
Epistaxis	No difference between TA and placebo		NR	

Clinical importance		Clinical relevance
E-aminocaproic acid 2.5 g		
Wormald grading scale	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	5: Evidence confined to unproven surrogate outcomes.
Boezaart grading scale	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	5: Evidence confined to unproven surrogate outcomes.
Epistaxis	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Tranexamic acid 100 mg		
Wormald grading scale	1: Clinically important *benefit*, confidence limit does not include null value ($p<0.05$)	5: Evidence confined to unproven surrogate outcomes.
Boezaart grading scale	1: Clinically important *benefit*, confidence limit does not include null value ($p<0.05$)	5: Evidence confined to unproven surrogate outcomes.
Epistaxis	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Tranexamic acid 1 g		
Wormald grading scale	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	5: Evidence confined to unproven surrogate outcomes.
Boezaart grading scale	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	5: Evidence confined to unproven surrogate outcomes.
Epistaxis	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in endoscopic sinus surgery using topical agents so likely to only be generalisable to this select population.		
Applicability		
Study conducted in Australia so likely to be applicable to the Australian/New Zealand setting.		
Comments		

Abbreviations: ACA, aminocaproic acid; ESS, endoscopic sinus surgery; ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; TA, Tranexamic acid.

STUDY DETAILS				
Citation				
Berenholtz SM, Pham JC, Garrett-Mayer E et al (2009)				
Affiliation/Source of funds				
John Hopkins University School of Medicine; Blomberg School of Public Health; Medical University of South Carolina. Federal funds received in support of this work.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital (single-centre)	
Intervention		Comparator		
E-aminocaproic acid 100 mg/kg administered immediately following anaesthesia followed by an infusion 10 mg/kg/hr continued for 8 hours after surgery		Placebo		
Population characteristics				
Aged > 18 years; diagnosis of scoliosis, kyphosis, kyphoscoliosis, pseudarthrosis, spinal stenosis or spondylothesis undergoing one of the following surgical procedures: anterior spinal fusion, posterior spinal fusion, anterior-posterior spinal fusion or osteotomy.				
Length of follow-up		Outcomes measured		
Up to postoperative day 8		Primary outcomes: total allogeneic RBC transfusion and postoperative RBC transfusion Secondary outcomes: blood loss, other transfusion requirements, laboratory results, complications, length of stay, cost.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Computer generated block randomisation, stratified by surgeon.	Intraoperative blood loss determined by anaesthesiologist.	Double-blind. All study personnel, patients and care providers blinded. Adequacy of blinding tested by surveying staff to test their ability to determine allocation (κ=0.06; P=0.72)	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	All patients included in analysis. Similar proportions did not receive allocated intervention (6 in each arm)
Overall quality assessment (descriptive)				
Good. Secure method of randomisation used, double-blinding secure, all patients included in analysis.				
RESULTS				
Outcome	Intervention group N=91	Comparator group N=91	Statistical significance	
E-aminocaproic acid 100 mg/kg				
	Mean ± SD	Mean ± SD	P value	
Total allogeneic RBC transfusion (units)	5.9 ± 4.7	6.9 ± 5.4	0.18	
Postoperative RBC transfusion (units)	2.0 ± 1.8	2.8 ± 2.8	0.03	
Total autologous RBC transfusion (units)	0.4 ± 1.1	0.6 ± 1.4	0.27	
Total allogeneic and autologous RBC transfusion (units)	6.4 ±4.9	7.6 ± 5.5	0.12	
Total FFP transfusion (units)	2.8 ± 3.9	3.5 ± 6.0	0.37	
Total platelets transfusion (units)	1.2 ± 3.1	1.2 ± 4.8	0.23	

Total blood products transfused (units)	10.4 ± 10.8	13.0 ±14.9	0.17
	Mean ± SD	Mean ± SD	P value
Intraoperative blood loss (mL)	2938 ± 2315	3273 ± 2195	0.32
Post-surgery to POD 1 blood loss (mL)	3265 ± 2416	3695 ± 2341	0.23
	n/N (%)	n/N (%)	P value
In-hospital mortality	0/91 (0)	1/91 (1.1)	0.32
Deep vein thrombosis	0/91 (0)	2/91 (2.2)	0.16
Cerebral infarction/transient ischaemic attack	0/91 (0)	1/91 (1.1)	0.32
Myocardial infarction	0/91 (0)	0/91 (0)	NA
Pulmonary embolism	1/91 (1.1)	3/91 (3.3)	0.31
Acute renal failure	1/91 (1.1)	1/91 (1.1)	1.00
Any thrombotic complication	2/91 (2.2)	6/91 (6.6)	0.15
Re-operation due to bleeding	0/91 (0)	2/91 (2.2)	0.16
	Mean ± SD	Mean ± SD	P value
ICU length of stay (days)	1.8 ± 1.6	2.8 ± 4.6	0.04
Hospital length of stay (days)	8.5 ± 3.9	9.5 ± 8.6	0.32
Total hospital charges (US$)	62,344 ± 27,497	68,670 ± 32,141	0.16

Clinical importance	Clinical relevance
E-aminocaproic acid 100 mg/kg	
Transfusion volume	1: Patient-relevant clinical outcome.

Total allogeneic RBC transfusion
4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect
Postoperative RBC transfusion
1: Clinically important *benefit*, confidence limit does not include null value (p=0.03)
Total autologous RBC transfusion
4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect
Total allogeneic and autologous RBC transfusion
4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect
Total FFP transfusion
4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect
Total plasma transfusion
4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect
Total blood products transfusion
4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect

Blood loss	*Intraoperative blood loss* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Post-surgery to POD 1 blood loss* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Mortality	*In-hospital mortality* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Morbidity	*Deep vein thrombosis* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Cerebral infarction/transient ischaemic attack* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Myocardial infarction* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Pulmonary embolism* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Acute renal failure* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Any thrombotic complication* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Re-operation due to bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Other	*ICU length of stay (days)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.04) *Hospital length of stay (days)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Total hospital charges (US$)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in certain types of spinal surgery which are known to result in the most bleeding (ie, anterior spinal fusion, posterior spinal fusion, anterior-posterior spinal fusion or osteotomy) so likely to only be generalisable to this select population.		
Applicability		

Study conducted in the US so may not be completely applicable to the Australian/New Zealand setting.
Comments
The authors note that the study was not sufficiently powered to show a difference between ε-aminocaproic acid and placebo. They state that due to the variability between results (which may have related to differences in clinical practice between the individual surgeons involved) a sample size of approximately 1088 would have been required to show a 1-unit reduction in total RBC transfusion.

Abbreviations: FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; POD, postoperative day; RBCs, red blood cells; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS				
Citation				
Chen CC, Wang CC, Wang, CP et al (2008) Prospective, randomized, controlled trial of tranexamic acid in patients who undergo head and neck surgery. Otolaryngology – Head and Neck Surgery 138: 762-767.				
Affiliation/Source of funds				
Department of Otolaryngology and Hematology Division, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei; Department of Information Technology, Overseas Chinese Institute of technology, Taichung, Taiwan. Supported by a grant from Taichung Veterans General Hospital.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital (single-centre)	
Intervention		Comparator		
Tranexamic acid: preoperative dose of IV TXA 10 mg/kg followed by continuous infusion of 1 mg/kg/hr during the operation.		Placebo: regimen as per tranexamic acid		
Population characteristics				
Aged 20-80 years; scheduled to undergo head and neck surgery. Mean age ~ 48; BMI ~24.5; 44% female.				
Length of follow-up		Outcomes measured		
Hospitalisation period.		Primary outcome: drainage duration Secondary outcome: drainage volume (blood loss); perioperative bleeding Other outcomes: hospitalisation, coagulation profiles		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Computer-generated randomisation list. Treatment prepared by staff not involved in the study.	Results determined by anaesthetist not aware of treatment assignment. Standard statistical methods used.	Double-blind. Neither patient not the anaesthetist assessing results aware of treatment assignment.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	5 patients excluded from analysis following randomisation (3 treatment/2 control)
Overall quality assessment (descriptive)				
Fair. 5/60 (8%) subjects excluded from analysis post-randomisation (3 in treatment group and 2 in control group). These subjects were not further described.				
RESULTS				
Outcome	Intervention group N=26	Comparator group N=29	Statistical significance	
Tranexamic acid				
	Mean ± SD	Mean ± SD	P value	
Perioperative bleeding (mL)	86.5 ± 128.5	115.5 ± 120.3	0.392	
Drainage amount (mL)	49.7 ± 32.6	88.8 ± 89.9	0.041	
	n/N (%)	n/N (%)	P value	
Deep vein thrombosis	0/26 (0)	0/29 (0)	NA	
	Mean ± SD	Mean ± SD	P value	
Length of hospital stay (days)	4.81 ± 0.80	5.31 ± 1.26	0.087	
Clinical importance		Clinical relevance		
Tranexamic acid				

Blood loss	*Perioperative bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Drainage amount* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.041)	1: Patient-relevant clinical outcome.
Morbidity	*Thrombosis* No events in either group	1: Patient-relevant clinical outcome.
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in patients undergoing head and neck surgery so likely to only be generalisable to this select population.		
Applicability		
Study conducted in a single centre in Taiwan so may not be completely applicable to the Australian/New Zealand setting.		
Comments		
The authors note that head and neck surgery generally results in less blood loss than cardiac and orthopaedic surgery so that tranexamic acid may not be as efficacious is head and neck surgery. Study was underpowered to detect a difference as powered based on blood loss seen in orthopaedic surgery.		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; ITT, intention-to-treat; IV, intravenous; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Choi WS, Irwin MG, Samman N (2009) The effect of tranexamic acid on blood loss during orthognathic surgery: a randomized controlled trial. J Oral Maxillofac Sug 67: 125-133.				
Affiliation/Source of funds				
Faculty of Dentistry and Medicine, University of Hong Kong, Hong Kong, P. R. China. Funding not reported.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital (single-centre)	
Intervention		Comparator		
Tranexamic acid: 20 mg/kg immediately prior to surgery		Placebo: regimen as per tranexamic acid		
Population characteristics				
Aged 16-40 years; scheduled for bimaxillary osteotomy at Queen Mary Hospital; ASA class I[a]. Mean age ~ 23 years, 66% female; mean weight ~57 kg.				
Length of follow-up		Outcomes measured		
Hospitalisation period.		Blood loss; patients requiring transfusion; length of hospital stay; haematology.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Computer-generated randomisation list/sealed envelopes. Treatment prepared by surgeon not involved in the study and then transferred to anaesthetist.	Results determined by anaesthetist not aware of treatment assignment. Standard statistical methods used. Blood analysis adjusted for operation time.	Double-blind. Neither patient nor the anaesthetist, surgeon or nurse aware of treatment assignment.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	12 patients (16%) excluded from analysis following randomisation (7 treatment/5 control)
Overall quality assessment (descriptive)				
Fair. 12/73 (16%) subjects excluded from analysis post-randomisation (7in treatment group and 5 in control group). These subjects were not further described.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Tranexamic acid				
	n/N (%)	n/N (%)	P value	
Transfusion incidence	4/32 (12.5)	7/29 (24.1)	0.32 *(post-hoc)*	
	Mean ± SD	Mean ± SD	P value	
Intraoperative blood loss during anterior mandibular surgery (mL)	277.0 ± 211.7 N=21	415.9 ± 314.2 N=23	NS	
Intraoperative blood loss during maxillary surgery (mL)	428.0 ± 233.3 N=32	643.8 ± 430.0 N=29	<0.05	
Intraoperative blood loss during ramus surgery (mL)	287.0 ± 216.3 N=24	329.3 ± 233.4 N=17	NS	
Total intraoperative blood loss (mL)	878.6 ± 577.7 N=32	1257 ± 817.8 N=29	<0.05	
	n/N (%)	n/N (%)	P value	
Thrombosis	0/32(0)	0/29 (0)	NA	
	Mean ± SD	Mean ± SD	P value	

Length of hospital stay (days)	7.2 ± 2.1	7.5 ± 2.3	0.32
Clinical importance		Clinical relevance	
Tranexamic acid			
Transfusion incidence	*Transfusion incidence* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.	
Blood loss	*Anterior mandibular surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect Maxillary surgery 1: Clinically important *benefit*, confidence limit does not include null value ($p<0.05$) *Ramus surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Total* 1: Clinically important *benefit*, confidence limit does not include null value ($p<0.05$)	1: Patient-relevant clinical outcome.	
Morbidity	*Thrombosis* No events in either group	1: Patient-relevant clinical outcome.	
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.	
EXTERNAL VALIDITY			
Generalisability			
Study conducted specifically in patients classified as ASA I undergoing orthognathic surgery (bimaxillary osteotomy) so likely to only be generalisable to this select population.			
Applicability			
Study conducted in a single centre in Hong Kong so may not be completely applicable to the Australian/New Zealand setting.			
Comments			
The authors did not measure postoperative bleeding as no suction drains were used in intraoral wounds so there may have been significant concealed blood loss during the early postoperative period which has not been accounted for.			

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: ASA, American Society of Anaesthesiologist; ITT, intention-to-treat; NS, not significant; RCT, randomised controlled trial; SD, standard deviation.
[a] A system used by anaesthesiologists to stratify severity of patients' underlying disease and potential for suffering complications from general anaesthesia . American Society of Anesthesiology (ASA) patient classification status defined as follows: ASA I – normal healthy patient; ASA II – patient with mild systemic disease; no functional limitation; ASA III – patient with severe systemic disease; definite functional impairment; ASA IV – patient with severe systemic disease that is a constant threat to life; ASA V – unstable moribund patient who is not expected to survive 24 hours with or without the operation; ASA VI –brain-dead patient whose organs are removed for donation to another ; E – emergency operation of any type, which is added to any of the 6 above categories.

STUDY DETAILS				
Citation				
Colwell Jr CW, Chelly JE, Murkin JM, Stevens D, O'Keefe TJ, Hall R, Parvizi J (2007) Randomized study of aprotinin effect on transfusions and blood loss in primary THA. Clinical Orthopaedics and Related Research 465: 189-195.				
Affiliation/Source of funds				
Shiley Centre for Orthopaedic Research & Education at Scripps Clinic, La Jolla, CA; the Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, PA; The department of Anesthesia, London Health Sciences Centre-UC, University of Western Ontario, Ontario Canada; Grand River Hospital, Kitchener, Ontario, Canada; Michigan Orthopaedic Centre, Ypsilanti, MI; the Department of Anesthesiology, Queen Elizabeth II Health Sciences Centre, Halifax Infirmary, Halifax, Nova Scotia, Canada; and the Roman Institute, Philadelphia, PA.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital	
Intervention		Comparator		
Aprotinin: loading dose 2 million KIU followed by 0.5 million KIU per hours until the end of surgery.		Placebo: saline (regimen as per aprotinin)		
Population characteristics				
Adult patients undergoing elective, unilateral, primary THA; > 18 years. Mean age 64 years; female 51%.				
Length of follow-up		Outcomes measured		
Hospitalisation period		Blood loss, transfusion requirements, ICU stay.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised using computer-generated codes and managed by IVRS.	Standard statistical methods used.	Described as double-blind. Patient and staff unaware of treatment assignment.	No evidence that there may be treatment/measurement bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Good. Random treatment allocation, double-blind, all patients included in analysis, large trial.				
RESULTS				
Outcome	Intervention group N=175	Placebo N=177	Statistical significance	
Aprotinin (IV)				
	n/N (%)	n/N (%)	P value	
Transfusion incidence (whole blood or RBCs)	30/175 (17)	57/177 (32)	0.0009	
Transfusion incidence (allogeneic blood)	19/175 (11)	39/177 (22)	0.006	
Transfusion incidence (whole blood or RBCs without donation)	18/140 (13)	33/138 (24)	0.02	
Transfusion incidence (whole blood or RBCs with donation)	12/37 (32)	23/37 (62)	ND (small sample size)	
	Mean ± SD	Mean ± SD	P value	
Transfusion volume (whole blood or RBCs; units)	0.27[a]	0.63[a]	0.0003	
Transfusion volume (allogeneic blood; units)	0.17[a]	0.42[a]	0.004	
Transfusion volume (whole blood or RBCs without donation; units)	0.21[a]	0.46[a]	0.0153	

Transfusion volume (whole blood or RBCs with donation; units)	0.52 [a]	1.21 [a]	ND (small sample size)
	LSM (95% CI)	LSM (95% CI)	P value
Intraoperative blood loss (mL)	331 (297, 368)	385 (346, 429)	0.0217
0-6 hr drainage (mL)	96 (72, 129)	177 (133, 235)	0.0003
Total drainage (mL)	276 (216, 353)	390 (307, 494)	0.0141
Total fluid loss (mL)	709 (618, 813)	957 (837, 1092)	0.0002
	n/N (%)	n/N (%)	P value
Mortality	0/175 (0)	1/177 (0.6)	NS
Deep vein thrombosis	2/175 (1.1)	3/177 (1.7)	NS
Pulmonary embolism	2/175 (1.1)	2/177 (1.1)	NS
Myocardial infarction	1/175 (0.6)	1/177 (0.6)	NS
Renal failure	2/175 (1.1)	2/177 (1.1)	NS
Clinical importance		Clinical relevance	
Aprotinin (IV)			
Transfusion incidence	*Whole blood or RBCs* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0009) *Allogeneic blood* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.006) *Whole blood or RBCs (– donation)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.02) *Whole blood or RBCs (+ donation)* 1: Clinically important *benefit*, confidence limit does not include null value (p=ND)	1: Patient-relevant clinical outcome.	
Transfusion volume	*Whole blood or RBCs* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0003) *Allogeneic blood* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.004) *Whole blood or RBCs (– donation)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0153) *Whole blood or RBCs (+ donation)* 1: Clinically important *benefit*, confidence limit does not include null value (p=ND)	1: Patient-relevant clinical outcome.	

Blood loss	*Intraoperative* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0217) *0-6 hr drain* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0003) *Total drainage* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0141) *Total fluid loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.0002)	1: Patient-relevant clinical outcome.
Mortality	*Mortality* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Deep vein thrombosis	Deep vein thrombosis 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Pulmonary embolism	Pulmonary embolism 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*Myocardial infarction* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Renal failure	*Renal failure* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing total hip arthroplasty so likely to be generalisable to this surgical population.		
Applicability		
Study conducted in the US and Canada so likely to be applicable to the Australian/New Zealand setting.		
Comments		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: CABG, coronary artery bypass graft; FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; IVRS, interactive voice response system; LSM, least squares mean; ND, not determined; NS, not significant; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation.
[a] Calculated post-hoc. Approximation based on the proportion of patients who received 1, 2, 3 or 4 units of transfusion.

STUDY DETAILS				
Citation				
Elwatidy S, Jamjoon Z, Elgamal E et al (2008) Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. Spine 33(24): 2577-2580.				
Affiliation/Source of funds				
Division of Neurosurgery and Department of Anaesthesia, College of Medicine King Aaud University, Riyadh, Saudi Arabia. Funded by CRMC, College of Medicine, King Saud University. Drug and placebo provided by pharmacy department King Khalid University Hospital.				
Study design	Level of evidence	Location/setting		
Double-blind RCT	II	Hospital (single-centre)		
Intervention	Comparator			
Tranexamic acid: loading dose of 2 g (adults) or 30 mg/kg (children) followed by continuous infusion of 100 mg/hr (adults) or 1 mg/hr/kg (children) during surgery and 5 hours following surgery.	Placebo: 0.9% saline; regimen as per tranexamic acid			
Population characteristics				
Patients (adults or children) undergoing spine surgery with expectant significant blood loss. Mean age ~ 50 years, 39% female; mean weight ~71 kg.				
Length of follow-up	Outcomes measured			
Up to 12 months – 3 years.	Blood loss; patients requiring transfusion; transfusion volume; length of hospital stay; haematology.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised using odd/even numbers. Treatment prepared by pharmacy staff who did not know patients.	Anaesthetist and surgeon unaware of treatment assignment. Standard statistical methods used.	Double-blind. Neither patient, the anaesthetist or surgeon aware of treatment assignment.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	All 64 randomised patients included in analysis.
Overall quality assessment (descriptive)				
Fair. Non-secure method of randomisation used (odd/even numbers). Study double-blind. All patients included in analysis.				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Tranexamic acid				
	n/N (%)	n/N (%)	P value	
Transfusion incidence	4/32 (12.5)	12/32 (37.5)	0.021	
	Mean ± SD	Mean ± SD	P value	
Amount of transfusion (mL)	93.75 ± 267.53	531.25 ± 1275.94	0.008	
Units transfused/patient (transfused patients only)	1.5	2.8[a]	NA	
Intraoperative blood loss (mL)	311.25 ± 412.49	584.69 ± 797.30	0.03	
Wound drain blood loss (mL)	97.94 ± 136.28	215.31 ± 276.04	0.004	
Total blood loss (mL)	406.13 ± 495.31	800.00 ± 1034.25	0.007	
	n/N (%)	n/N (%)	P value	
Thrombosis	0/32(0)	0/32 (0)	NA	
	Mean ± SD	Mean ± SD	P value	
Length of hospital stay (days)	8.45 ± 5.79	10.69 ± 8.27	0.21	
	Mean ± SD	Mean ± SD	P value	
Postoperative haemoglobin (g/dL)	12.39 ± 1.28	11.35 ± 1.57	0.006	
Clinical importance		Clinical relevance		
Tranexamic acid				

Transfusion incidence	*Transfusion incidence* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.021)	1: Patient-relevant clinical outcome.
Transfusion volume	*Amount of transfusion* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.008)	1: Patient-relevant clinical outcome.
Blood loss	*Intraoperative blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.03) *Wound drain blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.004 *Total blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.007)	1: Patient-relevant clinical outcome.
Morbidity	*Thrombosis* No events in either group	1: Patient-relevant clinical outcome.
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
Haemoglobin	*Postoperative haemoglobin* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05)	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult and paediatric patients classified undergoing spine surgery (so likely to only be generalisable to this select surgical population.		
Applicability		
Study conducted in a single centre in Saudi Arabia so may not be completely applicable to the Australian/New Zealand setting.		
Comments		
The authors used a larger than usual dose of tranexamic acid in this study in both adults and children. They state that there were no haemodynamic disturbances, apparent thromboembolic events, or other drug disturbances (including disturbed colour vision, numbness or weakness, confusion or allergic reaction) associated with its use. However, the small sample size should be noted when assessing the safety of this dose of tranexamic acid.		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: ITT, intention-to-treat; NA, not applicable; NS, not significant; RCT, randomised controlled trial; SD, standard deviation.
[a] One patient received 14 units of blood. If this person is excluded the mean units of blood transfused per transfused patient is 1.8.

STUDY DETAILS		
Citation		
Fawzy H, Elmistekawy E, Bonneau D et al (2009) Can local application of tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. Journal of Cardiothoracic Surgery 4:25.		
Affiliation/Source of funds		
Division of Cardiovascular and Thoracic Surgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada. Not funded.		
Study design	Level of evidence	Location/setting
Double-blind RCT	II	Hospital (single-centre) located in Saudi Arabia (West Armed Forces Hospital, Tabuk)

Intervention	Comparator
Tranexamic acid: 1 g TXA diluted in 100 ml normal saline applied locally into the pericardial and mediastinal cavities.	Placebo: 100 mL normal saline; regimen as per tranexamic acid
Population characteristics	
Patients scheduled for primary isolated elective CABG. Mean age ~ 57 years, 5% female; mean weight ~72 kg.	
Length of follow-up	Outcomes measured
Hospitalisation period	Blood loss; transfusion volume; length of hospital stay; haematology.

INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised using random numbers table. Treatment prepared by research pharmacist who delivered to operating room.	Staff measuring outcomes unaware of treatment assignment. Standard statistical methods used.	Double-blind. Neither the patient, surgeon, anaesthetist, scrub nurse nor perfusionist knew treatment assignment.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	All 38 randomised patients included in analysis.
Overall quality assessment (descriptive)				
Good. Random treatment allocation, double-blind, all patients included in analysis.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Tranexamic acid (topical)			
	Median	Median	P value
Postoperative transfusion of pRBCs (units)	1	1	0.82
Postoperative transfusion of FFP (units)	0	2	0.42
Postoperative transfusion of platelets (units)	0	2	0.03
24-hour chest-tube loss (mL)	626	1040	0.04
Total chest-tube loss (mL)	656 (range 248-2105)	1056 (range 210-3010)	NR
	n/N (%)	n/N (%)	P value
In-hospital mortality	0/19(0)	0/19 (0)	NA
Re-operation for bleeding	1/19 (5.3)	0/19 (0)	NR
In-hospital myocardial infarction	0/19(0)	0/19 (0)	NA
	Mean ± SD	Mean ± SD	P value
Length of hospital stay (days)	7.5 ± 3	7.8 ± 2	0.68
Length of ICU stay (hours)	29 ± 26	49 ± 20	0.02

Postoperative haemoglobin (g/dL)	10 ± 1.3	10 ± 1.3	0.39
Clinical importance		Clinical relevance	
Tranexamic acid (topical)			
Transfusion volume	*Postoperative pRBCs* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative FFP* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative platelets* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.03)	1: Patient-relevant clinical outcome.	
Blood loss	*24-hour chest-tube loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.04) *Total chest-tube loss* NR	1: Patient-relevant clinical outcome.	
Mortality	*In hospital mortality* No events in either group	1: Patient-relevant clinical outcome.	
Morbidity	*Re-operation for bleeding* NR *Myocardial infarction* No events in either group	1: Patient-relevant clinical outcome.	
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.	
Length of ICU stay	*Length of ICU stay* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.02)	2: Predictive surrogate outcome.	
Haemoglobin	*Postoperative haemoglobin* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.	
EXTERNAL VALIDITY			
Generalisability			
Study conducted specifically in patients undergoing primary CABG so likely to only be generalisable to this select surgical population. The authors note that their strict inclusion/exclusion criteria, small sample size and surgical methods used may further limit the generalisability of the results within the population of patients undergoing CABG.			
Applicability			
Study conducted in a single centre in Saudi Arabia so may not be completely applicable to the Australian/New Zealand setting.			
Comments			

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: CABG, coronary artery bypass graft; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; NA, not applicable; NR, not reported; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Gharabaghian M, Eghtesadi-Araghi P (2006) The efficacy of epsilon-aminocaproic acid and its timing in reducing blood loss in major cardiac coronary bypass surgery: a randomized double-blinded placebo-controlled study. International journal of Pharmacology 2(1): 131-135.				
Affiliation/Source of funds				
Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran; Parsteb Pajouheshyar Medical Sciences Research Institute, Tehran, Iran Funding not stated.				
Study design	Level of evidence	Location/setting		
RCT	II	Hospital (single-centre)		
Intervention	Comparator			
ε-aminocaproic acid administered using two different regimens: (i) Post-heparin group – normal saline pre-incision and post-incision and ACA at 150 mg/kg over 10 minutes after heparin injection and 15 mg/kg/hr from three minutes following heparin injection to the end of CPB; (ii) Pre-incision group – 150 mg/kg over 10 mins as pre-incision bolus, 15 mg/kg/hr as post-incision infusion and saline as post-heparin and 15 mg/kg/hr ACA as 3 min following heparin to end of CPB.	Placebo			
Population characteristics				
Aged > 18 years; undergoing primary CABG requiring at least 4 grafts with CPB.				
Length of follow-up	Outcomes measured			
Not stated	Blood loss (chest-tube drainage)			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised. No method reported.	Blood loss determined by chest-tube drainage at 6 hrs, 12 hrs and on removal of drainage.	Double-blinding stated. No further details provided.	Unclear if there was potential for treatment or measurement bias.	Assumed that all patients included in analysis.
Overall quality assessment (descriptive)				
Fair. Unclear if treatment allocation robust or full follow-up of patients.				
RESULTS				
Outcome	Intervention group N=20 (each group)	Comparator group N=20	Statistical significance	
E-aminocaproic acid (post-heparin group)				
	Mean ± SD	Mean ± SD	P value	
6-hr chest tube loss (mL)	~300 ± NR	~600 ± NR	<0.05	
12-hr chest tube loss (mL)	~500 ± NR	~650 ± NR	>0.05	
Final chest tube loss (mL)	~800 ± NR	~2000 ± NR	<0.05	
E-aminocaproic acid (pre-incision group)				
	Mean ± SD	Mean ± SD	P value	
6-hr chest tube loss (mL)	~300 ± NR	~600 ± NR	<0.05	
12-hr chest tube loss (mL)	~500 ± NR	~650 ± NR	>0.05	
Final chest tube loss (mL)	~1000 ± NR	~2000 ± NR	<0.05	
Clinical importance		Clinical relevance		
E-aminocaproic acid (post-heparin group)				

Blood loss	*6-hr chest tube loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05) *12-hr chest tube loss* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Total chest tube loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05)	1: Patient-relevant clinical outcome.
E aminocaproic acid (pre-incision group)		
Blood loss	*6-hr chest tube loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05) *12-hr chest tube loss* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Total chest tube loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05)	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted in patients undergoing major CABG surgery so likely to be generalisable to this population only.		
Applicability		
Study conducted in Iran so may not be applicable to the Australian/New Zealand setting.		
Comments		
The authors note that there was no difference in chest tube blood loss between the two different ε-aminocaproic acid regimens.		

Abbreviations: ACA, aminocaproic acid; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS				
Citation				
Grant MC, Kon Z, Joshi A, Christenson E, Kallam S, Burris N, Gu J, Poston RS (2008) Is aprotinin safe to use in a cohort at increased risk for thrombotic events: results from a randomized, prospective trial in off-pump coronary artery bypass. Ann Thorac Surg 86: 815-822.				
Affiliation/Source of funds				
Division of Cardiac Surgery, Department of Surgery, University of Maryland Medical System, University of Maryland, Baltimore County, Baltimore, Maryland, US.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital	
Intervention		Comparator		
Aprotinin: loading dose 2 million KIU followed by 0.5 million KIU per hours until the end of surgery.		Placebo: saline (regimen as per aprotinin)		
Population characteristics				
Adult patients undergoing off-pump coronary artery bypass surgery. Baseline demographic data not reported. Intraoperative data similar between groups.				
Length of follow-up		Outcomes measured		
Up to 1 year		Renal function; blood loss; mortality; morbidity		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Computer-generated randomisation based on permuted blocks of 4.	Powered to detect major cardiac and cerebrovascular events (MACCE). Standard statistical methods used.	Described as double-blind. Placebo use; drug delivered to operating room in unlabelled bottle.	No evidence that there may be treatment/measurement bias.	130 randomised; 10 not analysed (5 each arm) due to intraoperative decision to use CPB. 4 patients did not receive CT angiographic follow-up.
Overall quality assessment (descriptive)				
Fair. Randomised, described as double-blind, no baseline demographics reported; 5 patients from each arm not included in analysis.				
RESULTS				
Outcome	Intervention group N=59	Placebo N=61	Statistical significance	
Aprotinin (IV)				
	Mean ± SD	Mean ± SD	P value	
Intraoperative blood loss (mL)	867 ± 413[a] 870 ± 383[b]	1252 ± 380	<0.02	
Postoperative blood loss (mL)	415 ± 330[a] 427 ± 171[b]	716 ± 336	<0.003	
	n/N (%)	n/N (%)	P value	
MACCE	7/59 (11.8)	21/61 (34.4)	<0.005	
1-year mortality	3/59 (5.1)	8/61 (13.1)	NS	
6-month acute occlusion	3/80 SVG (3.8)	8/90 SVG (8.9)	NS	
In-hospital stroke	0/59 (0)	1/61 (1.6)	NS	
In-hospital myocardial infarction	1/59 (1.7)	4/61 (6.6)	NS	
Postoperative acute kidney injury	27/59 (45.8)	15/61 (24.6)	<0.03	
Acute renal failure within 6 months	2/59 (3.4)	2/61 (3.3)	NS	

Clinical importance		Clinical relevance
Aprotinin (IV)		
Blood loss	*Intraoperative blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.02) *Postoperative blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.003)	1: Patient-relevant clinical outcome.
MACCE	MACCE 1: Clinically important *benefit*, confidence limit does not include null value (p<0.005)	1: Patient-relevant clinical outcome.
Mortality	*Mortality* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Stroke	In-hospital stroke 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*In-hospital myocardial infarction* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Renal effects	*Acute kidney injury* 1: Clinically important *harm*, confidence limit does not include null value (p<0.03) *Renal failure* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing off-pump coronary artery bypass so likely to be generalisable to this surgical population.		
Applicability		
Study conducted in the US so likely to be applicable to the Australian/New Zealand setting.		
Comments		
Authors note all cases of renal failure resolved without dialysis		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: ITT, intention-to-treat; IV, intravenous; MACCE, major adverse cardiac and cerebrovascular event; NS, not significant; RCT, randomised controlled trial; SD, standard deviation; SVG, saphenous vein graft.
[a] Patients with peak aprotinin levels > 271 KIU/mL.
[b] Patients with peak aprotinin levels < 271 KIU/mL.

STUDY DETAILS				
Citation				
Jabalami M, Zakeri K (2006) Evaluation of topical tranexamic acid on intraoperative bleeding in endoscopic sinus surgery. Iran J Med Sci 31(4): 221-223.				
Affiliation/Source of funds				
Department of Anesthesiology and Intensive Care, Alzahra General Hospital, Isafan University of Medical Sciences, Isfahan, Iran. Funding not stated.				
Study design	Level of evidence	Location/setting		
RCT	II	Hospital (single centre)		
Intervention	Comparator			
Tranexamic acid: 1 g diluted in 20 mL saline applied topically	Placebo – 20 mL saline applied topically			
Population characteristics				
Adult patients (18-55 years) undergoing elective endoscopic sinus surgery. Female 32%. Authors note no significant difference between groups in terms of age, MABP, preoperative pulse rate, duration of surgery and operation indications.				
Length of follow-up	Outcomes measured			
Intraoperative.	Intraoperative bleeding			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised. No further details provided.	No details provided on assessment of outcomes or statistical analysis.	Not stated but assumed to be blinded due to use of placebo.	Unclear due to lack of information provided on allocation and blinding.	Unclear. Assumed to be all patients.
Overall quality assessment (descriptive)				
Poor. Allocation concealment and blinding poorly reported. Assessment of outcomes poorly reported.				
RESULTS				
Outcome	Intervention group N=26	Comparator group N=30	Statistical significance	
Tranexamic acid (topical)				
	Mean ± SD	Mean ± SD	P value	
Intraoperative blood loss (mL)	174.0 ± 10.6	229.1 ± 23.8	<0.05	
Clinical importance		Clinical relevance		
Tranexamic acid (topical)				
Blood loss	*Intraoperative blood loss* 1: Clinically important *benefit*, confidence limit does not include null value ($p<0.05$)	1: Patient-relevant clinical outcome.		
EXTERNAL VALIDITY				
Generalisability				
Study conducted specifically in adult patients undergoing elective endoscopic sinus surgery so likely to be generalisable only to this select group of patients.				
Applicability				
Study conducted in a single centre in Iran so may not be applicable to the Australian/New Zealand setting.				
Comments				

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: ITT, intention-to-treat; MABP, mean arterial blood pressure; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Jimenez JJ, Iribarren JL, Lorente L et al (2007) Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized controlled trial. Critical care: 11 R117.				
Affiliation/Source of funds				
Intensive Care Department, Hematology Department, Research Unit, Cardiac Surgery Department and Biochemistry and Central laboratories, Hospital Universitario de Canarias, Ofra s/n La Cuesta, La Laguna, Spain. Funded by the Fundación Canaria de Investigación y Salud (FUNCIS)				
Study design	Level of evidence	Location/setting		
Double-blind RCT	II	Hospital (single-centre)		
Intervention	Comparator			
Tranexamic acid: 2g before and after intervention.	Placebo: 0.9% saline			
Population characteristics				
Adult patients undergoing elective CPB surgery; age 67 years, female 46%, BMI 28 mg/kg^2.				
Length of follow-up	Outcomes measured			
Hospitalisation period	Primary: inflammatory response and vasoplegic shock Secondary outcomes: inflammation, coagulation and fibrinolysis parameters			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomly assigned by independent pharmacists using a list of pseudorandomised numbers to receive coded infusions of either TXA or placebo.	Staff measuring outcomes unaware of treatment assignment. Standard statistical methods used.	Double-blind.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	All 50 randomised patients included in analysis.
Overall quality assessment (descriptive)				
Good. Random treatment allocation, double-blind, all patients included in analysis.				

RESULTS			
Outcome	Intervention group N=24	Comparator group N=26	Statistical significance
Tranexamic acid (IV)			
	n/N (%)	n/N (%)	P value
Incidence of RBC and plasma transfusion in first 4 hours	1/24 (4.2)	2/26 (7.6)	0.39
Incidence of RBC and plasma transfusion until chest tube withdrawal	9/24 (37.5)	19/26 (73.1)	0.01
Incidence of plasma transfusion until chest tube withdrawal	1/24 (4.2)	8/26 (30.8)	0.02
	Mean (95% CI)	Mean (95% CI)	P value
24-hour blood loss (mL)	464 (308, 620)	1037 (771, 1303)	<0.01
Total blood loss (mL)	835 (407, 1263)	1466 (1116, 1818)	<0.01
	n/N (%)	n/N (%)	P value
In-hospital mortality	0/24 (0)	0/26 (0)	NA
	Mean (95% CI)	Mean (95% CI)	P value
Length of hospital stay (days)	4.5 (3, 6)	4 (2, 5)	0.34
	Mean (95% CI)	Mean (95% CI)	P value

Length of ICU stay (hours)	3 (2, 5.5)	3.5 (2, 5)	0.96
Clinical importance		Clinical relevance	
Tranexamic acid (IV)			
Transfusion incidence	*4-hr RBCs and plasma* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Chest-tube withdrawal RBCs and plasma* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.01) *Chest-tube withdrawal plasma* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.02)	1: Patient-relevant clinical outcome.	
Blood loss	*24-hour blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.01) *Total blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.01)	1: Patient-relevant clinical outcome.	
Mortality	*In hospital mortality* No events in either group	1: Patient-relevant clinical outcome.	
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.	
Length of ICU stay	*Length of ICU stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.	
EXTERNAL VALIDITY			
Generalisability			
Study conducted specifically in adult patients undergoing CPB surgery so likely to only be generalisable to this select surgical population.			
Applicability			
Study conducted in a single centre in the Canary Islands (Spain) so may not be completely applicable to the Australian/New Zealand setting.			
Comments			
The study was stopped early due to the higher proportion of severe bleeding seen in the placebo group during follow-up.			

Note: All post-hoc calculations performed using GraphPad software.

Abbreviations: BMI, body mass index; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; pRBCs, packed red blood cells; RCT, randomised controlled trial; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Later AFL, Maas JJ, Engbers FHM et al (2009) Tranexamic acid and aprotinin in low- and intermediate risk cardiac surgery: a non-sponsored, double-blind, randomised placebo-controlled trial. European Journal of Cardiothoracic Surgery 36: 322-329.				
Affiliation/Source of funds				
Departments of Cardiothroacic Surgery, Anaesthesiology and Intensive Care Medicine, Lelds Universltair Medlsch Centrum (LUMC), The Netherlands. Funded by intramural sources only.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital (single-centre)	
Intervention		Comparator		
Tranexamic acid: 1g loading dose, 500 mg added to the CPB system p0rime, and a continuous infusion of 400 mg/hr. High dose aprotinin (Hammersmith protocol): 2 x 10^6 KIU aprotinin loading dose, 2 x 10^6 KIU added to the CPB system prime, and a continuous infusion of 5 x 10^5 KIU/h during CPB).		Placebo: 0.9% saline (regimen as per TXA)		
Population characteristics				
Adult patients undergoing first-time, non-complex (one or two procedures) heart surgery (ie, low to moderate risk) with the use of CPB. Mean age 65 years; female 30%, BMI 26.5 kg/m^2.				
Length of follow-up		Outcomes measured		
Hospitalisation period		Primary: total postoperative blood loss and transfusion requirements. Secondary: in-hospital mortality, re-exploration, perioperative myocardial infarction; mediastinitis, renal failure, neurological complications, sepsis, length of ICU and hospital stay.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Opaque envelopes prepared by independent statistician, medication prepared by independent anaesthesia assistant into syringes marked with patient number only.	Staff measuring outcomes unaware of treatment assignment. Standard statistical methods used.	Double-blind. All caretakers were blinded to medication allocation.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	35/333 (10.5%) patients randomised excluded from analysis, mostly due to patients who did not subsequently use CPB.
Overall quality assessment (descriptive)				
Good. Random treatment allocation, double-blind, not all patients included in analysis but reasonably large trial.				
RESULTS				
Outcome	Intervention group N=99 TXA N=96 aprotinin	Placebo N=103	Statistical significance	
Tranexamic acid (IV)				
	n/N (%)	n/N (%)	P value	
PRBC transfusion	57/99 (57.6)	73/103 (70.9)	0.057	
Blood products transfusion	69/99 (69.7)	81/103 (78.6)	0.15	
	Median (IQR)	Median (IQR)	P value	

Total units pRBCs transfused (units)	1.0 (2.0)	2.0 (3.0)	0.038
Total mediastinal chest tube loss (mL)	760 (540)	860 (740)	0.034
	n/N (%)	n/N (%)	P value
In-hospital mortality	1/99 (1.0)	1/103 (1.0)	1.00
Re-operation for any reason	14/99 (14.1)	14/103 (13.6)	1.00 *(post-hoc)*
Re-operation due to surgical bleeding	3/99 (3.0)	3/103 (2.9)	1.00 *(post-hoc)*
Re-operation due to non-surgical bleeding	2/99 (2.0)	4/103 (3.9)	0.68 *(post-hoc)*
Perioperative myocardial infarction	0/99 (0)	8/103 (7.8)	0.004
Renal failure by Mangano[a]	3/99 (3.0)	3/103 (2.9)	1.00 *(post-hoc)*
Renal complication RIFLE	8/99 (8.1)	18/103 (17.5)	0.059 *(post-hoc)*
Stroke	1/99 (1.0)	1/103 (1.0)	1.00 *(post-hoc)*
	Mean ± SD	Mean ± SD	P value
Length of hospital stay (days)	9.4 ± 8.6	8.5 ± 7.4	0.43 *(post-hoc)*
Length of ICU stay (hours)	49.2 ± 89.6	60.1 ± 116.6	0.46 *(post-hoc)*
High-dose aprotinin (IV)			
	n/N (%)	n/N (%)	P value
PRBC transfusion	48/96 (50.0)	73/103 (70.9)	0.004
Blood products transfusion	59/96 (61.5)	81/103 (78.6)	0.009
	Median (IQR)	Median (IQR)	P value
Total units pRBCs transfused (units)	0.5 (1.0)	2.0 (3.0)	<0.001
Total mediastinal chest tube loss (mL)	546 (405)	860 (740)	<0.001
	n/N (%)	n/N (%)	P value
In-hospital mortality	2/96 (2.1)	1/103 (1.0)	0.61 *(post-hoc)*
Re-operation for any reason	5/96 (5.2)	14/103 (13.6)	0.054 *(post-hoc)*
Re-operation due to surgical bleeding	4/96 (4.2)	3/103 (2.9)	0.71 *(post-hoc)*
Re-operation due to non-surgical bleeding	0/96 (0)	4/103 (3.9)	0.12 *(post-hoc)*
Perioperative myocardial infarction	1/96 (1.0)	8/103 (7.8)	0.023
Renal failure by Mangano[a]	3/96 (3.1)	3/103 (2.9)	1.0 *(post-hoc)*
Renal complication RIFLE	10/96 (10.4)	18/103 (17.5)	0.011
Stroke	1/96 (1.0)	1/103 (1.0)	1.0 *(post-hoc)*
	Mean ± SD	Mean ± SD	P value
Length of hospital stay (days)	7.8 ± 6.7	8.5 ± 7.4	0.49 *(post-hoc)*
Length of ICU stay (hours)	55.4 ± 134.2	60.1 ± 116.6	0.79 *(post-hoc)*

Clinical importance	Clinical relevance
Tranexamic acid (IV)	
Transfusion incidence *pRBCs* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Blood products* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.

Transfusion volume	*pRBCs* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.038)	1: Patient-relevant clinical outcome.
Blood loss	*Total mediastinal chest-tube loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.034)	1: Patient-relevant clinical outcome.
Mortality	*In hospital mortality* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*Myocardial infarction* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.007)	1: Patient-relevant clinical outcome.
Re-operation	*Any* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Surgical bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Non-surgical bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Renal failure	*Renal failure* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Renal complication	*Renal complication* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Stroke	*Stroke* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
Length of ICU stay	*Length of ICU stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
High-dose aprotinin (IV)		
Transfusion incidence	*pRBCs* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.004) *Blood products* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.009)	1: Patient-relevant clinical outcome.
Transfusion volume	*pRBCs* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.

Blood loss	*Total mediastinal chest-tube loss* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.
Mortality	*In hospital mortality* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*Myocardial infarction* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.023)	1: Patient-relevant clinical outcome.
Re-operation	*Any* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Surgical bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Non-surgical bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Renal failure	*Renal failure* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Renal complication	*Renal complication* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.011)	1: Patient-relevant clinical outcome.
Stroke	*Stroke* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
Length of ICU stay	*Length of ICU stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing first-time, non-complex CPB surgery so likely to only be generalisable to this select surgical population.		
Applicability		
Study conducted in a single centre in the Netherlands so may be applicable to the Australian/New Zealand setting.		
Comments		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, inter-quartile range; ITT, intention-to-treat; IV, intravenous; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.
[a] Mangano et al (2006) The risk associated with aprotinin in cardiac surgery. NEJM 354: 353-365.

STUDY DETAILS				
Citation				
Leijdekkers VJ, Vahl AC, Mackaay AJC, Huijgens PC, Rauwerda JA (2006) Aprotinin does not diminish blood loss in elective operations for infrarenal abdominal aneurysms: a randomized, double-blind controlled trial. Ann Vasc Surg 20: 322-329.				
Affiliation/Source of funds				
Department of Surgery, Onze Leve Vrouwe Gasthius, Amsterdam, The Netherlands; Department of Surgery, Meander Medical Center, Amersfoort, The Netherlands; Departments of Surgery and Haematology, Vrije Universitiet Medical Center, Amsterdam, The Netherlands.				
Study design	Level of evidence		Location/setting	
Double-blind RCT	II		Hospital	
Intervention		Comparator		
Aprotinin: Test dose of 500,000 KIU, followed by 2,000,000 KIU in 15 mins. During surgery patients received a continuous infusion of 500,000 KIU per hour, to a maximum of 2,000,000 KIU.		Placebo: 0.9% saline (regimen as per aprotinin)		
Population characteristics				
Adult patients undergoing infrarenal cross-clamping of the aorta and insertion of either an aortic tube or bifurcation prosthesis for asymptomatic infrarenal abdominal aneurysm. Mean age 68 years; female 20%.				
Length of follow-up		Outcomes measured		
Hospitalisation period		Blood loss, transfusion requirements, postoperative complications.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised using standard randomization list.	Standard statistical methods used.	Described as double-blind. List not to be opened until study inclusion finalised. No further details provided.	No details provided to assess possibility of treatment/measurement bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Fair. Random treatment allocation, double-blind but not well described, small trial.				
RESULTS				
Outcome	Intervention group N=16	Placebo N=19	Statistical significance	
Aprotinin (IV)				
	Mean ± SD	Mean ± SD	P value	
Mean total infusion (mL)	7845 ± 4888	7835 ± 4776	0.99	
Mean pRBCs transfused (units)	4.1 ± 3.1	4.1 ± 2.9	0.95	
Mean FFP transfused (units)	0.5 ± 0.9	0.3 ± 0.8	0.35	
Mean blood loss (mL)	2362 ± 1340	2466 ± 1370	0.88	
Mortality	1/16 (6.3)	1/19 (5.3)	1.00 *(post-hoc)*	
Re-operation for bleeding	1/16 (6.3)	1/19 (5.3)	1.00 *(post-hoc)*	
Clinical importance			Clinical relevance	
Aprotinin (IV)				

Transfusion volume	*Mean total infusion (mL)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Mean pRBCs (units)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Mean FFP (units)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Blood loss	*Mean blood loss (mL)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Mortality	*In hospital mortality* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Reoperation for bleeding	*In hospital mortality* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing elective surgery for infra-renal abdominal aneurysm so likely to only be generalisable to this select surgical population.		
Applicability		
Study conducted in the Netherlands so likely to be applicable to the Australian/New Zealand setting.		
Comments		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS				
Citation				
Maddali MM, Rajakumar MC (2007) Tranexamic acid and primary coronary artery bypass surgery: a prospective study. Asian Cardiovascular and Thoracic Annals 15: 313-319.				
Affiliation/Source of funds				
Departments of Anesthesia and Cardiothoracic Surgery, Royal Hospital, Muscat, Sultanate of Oman Funding not stated				
Study design	Level of evidence	Location/setting		
Double-blind RCT	II	Hospital (single-centre)		
Intervention	Comparator			
Tranexamic acid: 10 mg/kg loading dose before skin incision followed by a continuous infusion of 1 mg/kg/hr until commencement of protamine reversal after separation from CPB.	Placebo: normal saline (regimen as per TXA)			
Population characteristics				
Adult patients undergoing primary non-emergency CABG. Mean age 58, female 32%, weight 65 kg.				
Length of follow-up	Outcomes measured			
Hospitalisation period	Postoperative blood loss; transfusion requirements, re-operation, haematological profile, biochemical data, operative data.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomisation based on computer-generated code and sequentially numbered, sealed, opaque envelopes opened by a nurse in the operating room who prepared the infusions.	Staff measuring outcomes unaware of treatment assignment. Standard statistical methods used.	Double-blind. With the exception of the nurse who prepared the treatment, staff in the operating room and post-surgical unit were not aware of treatment assignment.	Staff blinded to treatment allocation so not likely to be treatment or measurement bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Good. Random treatment allocation, double-blind, all patients included in analysis.				
RESULTS				
Outcome	Intervention group N=111	Comparator group N=111	Statistical significance	
Tranexamic acid (IV)				
	Mean ± SD	Mean ± SD	P value	
Total pRBCs transfused (mL)[a]	608.6 ± 233.9	952.4 ± 292.1	0.001	
Total units FFP transfused	0.72 ± 1.9	1.6 ± 2.4	<0.01	
Total units platelets transfused	0.7 ± 1.9	0.8 ± 2.3	NS	
Total drainage (mL)	633.0 ± 183.2	980.9 ± 267.2	0.001	
	n/N (%)	n/N (%)	P value	
Re-operation due to bleeding	3/111 (2.7)	3/111 (2.7)	NS	
	Mean ± SD	Mean ± SD	P value	
Postoperative haemoglobin (g/dL)	10.1 ± 1.1	10.4 ± 1.3	NS	
Clinical importance		Clinical relevance		
Tranexamic acid (IV)				

Transfusion volume	*pRBCs* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001) *FFP* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.01) *Plasma* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Blood loss	*Total drainage* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001)	1: Patient-relevant clinical outcome.
Re-operation	*Re-operation due to bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Haemoglobin	*Postoperative haemoglobin* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing coronary artery bypass surgery so likely to only be generalisable to this select surgical population.		
Applicability		
Study conducted in a single centre in the Sultanate of Oman so may not be completely applicable to the Australian/New Zealand setting.		
Comments		
The authors note that as this was the only tertiary cardiac centre in the country, the surgeons involved in the study were at various stages of expertise and training and this might have led to higher than expected blood drainage and transfusion requirements.		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; CABG, coronary arterial bypass graft; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; NS, not significant; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.
[a] Article states units rather than mL, but amounts reported correspond to mL.

STUDY DETAILS				
Citation				
Mayur G, Purvi P, Ashoo G, Panjak D (2007) Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section: a randomized case controlled prospective study. The Journal of Obstetrics and Gynecology of India 57(3): 227-230.				
Affiliation/Source of funds				
Department of Obstetrics and Gynecology, Medical College and SSG Hospital, Gujarat, India. No pharmaceutical company funding				
Study design	Level of evidence		Location/setting	
Pseudo-RCT	II		Hospital (single-centre)	
Intervention		Comparator		
Tranexamic acid: 1 g (in 10 mL) IV over 5 minutes 20 minutes prior to incision.		No TXA		
Population characteristics				
Full term primiparas, multiparas with singleton pregnancy; mean age ~24, mean weight ~50 kg.				
Length of follow-up		Outcomes measured		
Hospitalisation period		Post-partum haemorrhage, vital signs, haemoglobin.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Pseudorandomised based on odd/even numbers.	Statistical methods not described.	Open-label	Objective measurements of volume and weight used for post-partum haemorrhage so should not be subject to bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Poor. Pseudo-randomisation using odd/even numbers (not very secure), open-label.				
RESULTS				
Outcome	Intervention group N=50	Comparator group N=50	Statistical significance	
Tranexamic acid (IV)				
2. Post-partum haemorrhage				
	Mean ± SD	Mean ± SD	P value	
Post-partum haemorrhage (placental delivery to end of surgery; mL)	299.21 ± 31.44	339.76 ± 28.86	0.056	
Post-partum haemorrhage (end of surgery to 2 hours post partum; mL)	75.71 ± 20.02	133.03 ± 14.68	0.001	
Post-partum haemorrhage (placental delivery to 2 hours post-partum; mL)	374.92 ± 51.46	472.79 ± 43.54	0.003	
Postoperative haemoglobin (g/dL)	NR	NR	NS	
	n/N (%)	n/N (%)	P value	
Thrombosis	0/50	0/50	NA	
Clinical importance			Clinical relevance	
Tranexamic acid (IV)				

Blood loss	*Placental delivery to end of surgery* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *End of surgery to 2 hours post-partum* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001) *Placental delivery to 2 hours post partum* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.003)	1: Patient-relevant clinical outcome.
Thrombosis	*Thrombosis* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Haemoglobin	*Postoperative haemoglobin* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in women delivering full-term, single pregnancies by lower segment caesarean section so generalisable only to this specific population.		
Applicability		
Study conducted in a single centre in India so may not be completely applicable to the Australian/New Zealand setting.		
Comments		
There was no significant difference in Apgar scores between the TXA and placebo arms (p=0.5).		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Mehr-Aein A, Sadeghi M, Madani-civi M (2007) Does tranexamic acid reduce blood loss in off-pump coronary artery bypass? Asian cardiovascular and Thoracic Annals 15: 285-289.				
Affiliation/Source of funds				
Department of Anaesthesiology, Shariati Hospital, Research Department, Tehran Heart Centre, Tehran University of Medical Sciences, Tehran, Iran.				
Study design	Level of evidence	Location/setting		
RCT	II	Hospital (single-centre)		
Intervention	Comparator			
Tranexamic acid: loading dose of 15 mg/kg administered at the beginning of surgery, with the same dose before the infusion of heparin, at the end of surgery and after protamine infusion.	Placebo – saline solution (same regimen as TXA)			
Population characteristics				
Undergoing primary CABG, aged ≤ 70 years, LVEF ≥ 35%, BMI ≤ 25, no aspirin for 7 days prior, no preoperative heparin infusion.				
Length of follow-up	Outcomes measured			
Hospitalisation period	Blood loss, haematologic and blood chemistry parameters, morbidity outcomes, mortality.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomly allocated. No further details provided. Drug prepared by pharmacy staff not involved in study into coded infusion syringes.	Outcomes assessed by clinical staff not aware of treatment assignment. Standard statistical methods used.	Double-blind. Staff in the operating room and ICU unaware of treatment assignment.	Staff unaware of treatment assignment so should not be treatment/measurement bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Good. Randomised, double-blind, all subjects included in analysis.				

RESULTS			
Outcome	Intervention group N=33	Comparator group N=33	Statistical significance
Tranexamic acid (IV)			
	n/N (%)	n/N (%)	P value
Transfusion incidence (whole blood or pRBC transfused)	5/33 (15.2)	8/33 (24.2)	0.07
Transfusion incidence (FFP transfused)	0/33 (0)	6/33 (18.2)	0.05
Transfusion incidence (platelets transfused)	0/33 (0)	0/33 (0)	NA
Transfusion incidence (total patients transfused)	5/33 (15.2)	12/33 (36.4)	0.09 *(post-hoc)*
	Mean	Mean	P value
Whole blood or pRBC transfused per patient (units)	0.46	0.94	0.001
	Mean ± SD	Mean ± SD	P value
Postoperative blood loss 0-2 hr (mL)	90 ± 25	180 ± 37	<0.001

Postoperative blood loss 2-6 hr (mL)	190 ± 41	290 ± 78	0.001
Total postoperative blood loss (mL)	320 ± 38	480 ± 75	0.001
	n/N (%)	n/N (%)	P value
Mortality	0/33	0/33	NA
Surgical re-exploration for bleeding	0/33 (0)	1/33 (3.0)	>0.05
Myocardial infarction	0/33	0/33	NA
Renal dysfunction (creatinine > 2 mg/dL)	0/33 (0)	1/33 (3.0)	>0.05
Hospital length of stay (days)	4.8 ± 0.4	4.8 ± 0.9	0.09
ICU length of stay (hours)	10 ± 1.8	12 ± 3.2	<0.05
First postoperative day haemoglobin (g/dL)	10.6 ± 1.9	10.4 ± 0.8	>0.05

Clinical importance		Clinical relevance
Tranexamic acid (IV)		
Transfusion incidence	*Whole blood or pRBC* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *FFP* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect (p=0.05) *Platelets* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05) *Any blood products* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Transfusion volume	*Whole blood or pRBC* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001)	1: Patient-relevant clinical outcome.
Blood loss	*Postoperative blood loss (0-2 hr)* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.01) *Postoperative blood loss (2-6 hr)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001) *Total drainage* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001)	1: Patient-relevant clinical outcome.
Mortality	*In-hospital mortality* No deaths in either treatment group	1: Patient-relevant clinical outcome.
Re-operation	*Re-operation for bleeding* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*Thrombosis* No MI in either treatment group	1: Patient-relevant clinical outcome.
Renal dysfunction	*Creatinine > 2 mg/dL* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.

Hospital length of stay	*Hospital length of stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
ICU length of stay	*ICU length of stay* 1: Clinically important *benefit*, confidence limit does not include null value ($p<0.05$)	2: Predictive surrogate outcome.
Haemoglobin	*First day postoperative haemoglobin* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in patients no older than 70 years who were undergoing primary CABG so likely to be generalisable only to this select group of patients.		
Applicability		
Study conducted in a single centre in Iran so may not be completely applicable to the Australian/New Zealand setting.		
Comments		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; LVEF, left ventricle ejection fraction; MI, myocardial infarction; NA, not applicable; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Mehraien A, Ghafari A, Mohammadi SS (2009) Effect of topical aprotinin on early postoperative bleeding and ICU stay after coronary artery bypass graft surgeries. Pakistan Journal of Biological Sciences 12(10): 813-816.				
Affiliation/Source of funds				
Department of Anaesthesiology, Tehran University of Medical Sciences, Dr Shariati Hospital, Tehran, Iran.				
Study design	Level of evidence	Location/setting		
Double-blind RCT	II	Hospital		
Intervention	Comparator			
Aprotinin: 500,000 KIU (50 mL) applied topically to the heart, pericardium and mediastinum prior to sterna closure.	Placebo: saline (regimen as per aprotinin)			
Population characteristics				
Adult patients undergoing first-time coronary artery bypass graft surgery; ASA physical status II or III; aged 50-70 years. Mean age 58 years; female 32%.				
Length of follow-up	Outcomes measured			
Hospitalisation period	Blood loss, transfusion requirements, ICU stay.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomised using computer-generated codes	Standard statistical methods used.	Described as double-blind. Coded syringes prepared by independent anaesthetist. Outcomes determined by blinded anaesthetist.	No evidence that there may be treatment/measurement bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Good. Random treatment allocation, double-blind, all patients included in analysis.				
RESULTS				
Outcome	Intervention group N=64	Placebo N=64	Statistical significance	
Aprotinin (topical)				
	Mean ± SD	Mean ± SD	P value	
Mean pRBCs transfused (units)	0.5 ± 0.7	1.7 ± 1.0	0.002	
24-hour chest tube loss (mL)	451 ± 218	707 ± 269	0.003	
ICU length of stay (hours)	48.8 ± 13.6	69.4 ± 16.6	0.001	
Clinical importance		Clinical relevance		
Aprotinin (topical)				
Transfusion volume	*Mean pRBCs (units)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.003)	1: Patient-relevant clinical outcome.		
Blood loss	*24-hour chest tube loss (mL)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.004)	1: Patient-relevant clinical outcome.		
ICU length of stay	*ICU length of stay (hours)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001)	1: Patient-relevant clinical outcome.		
EXTERNAL VALIDITY				
Generalisability				
Study conducted specifically in adult patients undergoing first-time CABG so likely to be generalisable to this surgical population.				

Applicability
Study conducted in Iran so may applicable to the Australian/New Zealand setting.
Comments

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: CABG, coronary artery bypass graft; FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS				
Citation				
Nurözler F, Kutlu T, Küçük G (2008) Aprotinin for patients exposed to clopidogrel before off-pump coronary bypass. Asian Cardiovascular and Thoracic Annals 16: 483-487.				
Affiliation/Source of funds				
Division of Cardiovascular Surgery, Central Hospital, Izmir, Turkey.				
Study design	Level of evidence	Location/setting		
Double-blind RCT	II	Hospital		
Intervention	Comparator			
Aprotinin: loading dose 1 million KIU followed by 0.5 million KIU per hour until the end of surgery.	Placebo: saline (regimen as per aprotinin)			
Population characteristics				
Adult patients who had received clopidogrel within 5 days of surgery undergoing off-pump coronary artery bypass surgery. Mean age 64 years; 27% female; BMI ~ 27 kg/m^2.				
Length of follow-up	Outcomes measured			
In hospital	Transfusion incidence; transfusion volume; blood loss; mortality; morbidity.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
List of random treatment codes generated by a biostatistician using a block design.	Standard statistical methods used.	Described as double-blind. Blinding of ICU staff described as being "conducted in an appropriate way".	No evidence that there may be treatment/measurement bias.	All subjects included in analysis.
Overall quality assessment (descriptive)				
Fair. Randomised, described as double-blind, similar at baseline; all patients included; small study.				
RESULTS				
Outcome	Intervention group N=25	Placebo N=26	Statistical significance	
Aprotinin (IV)				
	n/N (%)	n/N (%)	P value	
Transfusion incidence (RBCs)	17/25 (68)	23/26 (88)	0.014	
Transfusion incidence (blood products)	7/25 (28)	14/26 (53)	0.002	
	Mean ± SD	Mean ± SD	P value	
Transfusion volume (pRBCs; units)	1.7 ± 1.4	2.9 ± 1.8	0.014	
Transfusion volume (platelets; units)	0.4 ± 0.6	2.3 ± 1.2	0.002	
Transfusion volume (FFP; units)	0.6 ± 0.3	1.4 ± 0.6	0.008	
Drainage (mL/24 hr)	423 ± 178	748 ± 212	0.005	
	n/N (%)	n/N (%)	P value	
Re-operation	0/25 (0)	2/26 (7.7)	0.157	
In-hospital myocardial infarction	0/25 (0)	0/26 (0)	NA	
In-hospital stroke	1/25 (4.0)	0/26 (0)	0.317	
	Mean ± SD	Mean ± SD	P value	
ICU length of stay (hr)	28 ± 11	33 ± 10	0.153	
Hospital length of stay (days)	5.3 ± 1.6	5.5 ± 1.4	0.660	
Clinical importance		Clinical relevance		
Aprotinin (IV)				

Transfusion incidence	*Red blood cell* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.014) *Blood products* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.002)	1: Patient-relevant clinical outcome.
Transfusion volume (units)	*Mean pRBCs* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.014) *Mean platelets* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.002) *Mean FFP* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.008)	1: Patient-relevant clinical outcome.
Blood loss	*Drainage (mL/24 hr)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.005)	1: Patient-relevant clinical outcome.
Re-operation	*Re-operation* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Myocardial infarction	*Myocardial infarction* No events in either treatment arm.	1: Patient-relevant clinical outcome.
Stroke	Stroke 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
Length of stay	*ICU* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect *Hospital* 4: Range of estimates includes clinically important point estimate but also compatible with no effect, or a harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing off-pump coronary artery bypass who had been on clopidogrel within 5 days of surgery so likely to be generalisable to this surgical population.		
Applicability		
Study conducted in Turkey so may be applicable to the Australian/New Zealand setting.		
Comments		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; NS, not significant; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS				
Citation				
Sadeghi M, Mehr-Aein A (2007) Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A prospective randomised double-blind study in 67 patients. Acta Medica Iranica 45(6): 437-442.				
Affiliation/Source of funds				
Department of Anesthesiology, Shariati Hospital, School of Medicine/Medical Sciences, University of Tehran, Iran. Funding not reported.				
Study design	Level of evidence	Location/setting		
RCT	II	Hospital (single-centre)		
Intervention	Comparator			
Tranexamic acid: single bolus dose if 15 mg/kg before surgical incision.	Placebo – saline solution (same regimen as TXA)			
Population characteristics				
Patients with a diagnosis of fracture of the hip necessitation hip surgery (extracapsular fractures requiring plating and nailing and intracapsular fractures requiring hemiarthroplasty). Mean age ~48, female 40%, BMI ~23.				
Length of follow-up	Outcomes measured			
Hospitalisation period	Blood loss, transfusion incidence, transfusion volume, mortality, haematology			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Randomly allocated using a random number technique. Drug prepared by pharmacy staff not involved in study into coded infusion syringes.	Outcomes assessed by clinical staff not aware of treatment assignment. Standard statistical methods used.	Double-blind. Staff in the operating room and ICU unaware of treatment assignment.	Staff unaware of treatment assignment so should not be treatment/measurement bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Good. Randomised, double-blind, all subjects included in analysis.				
RESULTS				
Outcome	Intervention group N=32	Comparator group N=35	Statistical significance	
Tranexamic acid (IV)				
3. Transfusion incidence				
	n/N (%)	n/N (%)	P value	
Transfusion incidence (whole blood or pRBC transfused)	12/32 (37.5)	20/35 (57.1)	0.04	
Transfusion incidence (FFP transfused)	1/32 (3.1)	0/35 (0)	NS	
Transfusion incidence (platelets transfused)	0/33 (0)	0/33 (0)	NA	
Transfusion incidence (total patients transfused)	12/32 (37.5)	20/35 (57.1)	0.04	
	Mean	Mean	P value	
Whole blood or pRBC transfused per patient (units)	1.25	1.95	0.001	
	Mean ± SD	Mean ± SD	P value	
Perioperative blood loss (mL)	652 ± 228	1108 ± 372	0.003	
Postoperative blood loss 1 hr (mL)	111 ± 76	139 ± 100	0.39	

Postoperative blood loss 2 hr (mL)	192 ± 78	246 ± 113	0.28
Postoperative blood loss 5 hr (mL)	255 ± 59	323 ± 54	0.31
Postoperative blood loss 12 hr (mL)	296 ± 40	375 ± 30	0.20
Postoperative blood loss 24 hr (mL)	300 ± 54	390 ± 65	0.11
Total blood loss (mL)	960 ± 284	1484 ± 374	0.001
	n/N (%)	n/N (%)	P value
Mortality	0/32 (0)	1/35 (2.9)	NR
	Mean ± SD	Mean ± SD	P value
Hospital length of stay (days)	4.3 ± 1.6	5.8 ± 1.5	<0.05
Postoperative day haemoglobin (g/dL)	10.1 ± 1.4	8.9 ± 2.1	<0.05

Clinical importance	Clinical relevance
Tranexamic acid (IV)	
Transfusion incidence *Whole blood or pRBC* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.04) *FFP* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect (p<0.05) *Platelets* No patients in either group transfused with platelets *Any blood products* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.04)	1: Patient-relevant clinical outcome.
Transfusion volume *Whole blood or pRBC* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001)	1: Patient-relevant clinical outcome.

Blood loss	*Perioperative blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.003) *Postoperative blood loss (1 hr)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative blood loss (2 hr)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative blood loss (5 hr)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative blood loss (12 hr)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative blood loss (24 hr)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Total blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.001)	1: Patient-relevant clinical outcome.
Mortality	*In-hospital mortality* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Hospital length of stay	*Hospital length of stay* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05)	1: Patient-relevant clinical outcome.
Haemoglobin	*First day postoperative haemoglobin* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.05)	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in patients undergoing selected hip surgeries for particular hip fractures so likely to be generalisable only to this select group of patients.		
Applicability		
Study conducted in a single centre in Iran so may not be completely applicable to the Australian/New Zealand setting.		
Comments		
The authors note there was no difference in thrombotic complications, pulmonary dysfunction and neurological deficits however these are not quantified.		

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; NA, not applicable; NR, not reported; NS, not significant; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Sekhavat L, Tabatabah A, Dalili M et al (2009) Efficacy of tranexamic acid in reducing blood loss after cesarean section. The Journal of maternal-Fetal and Neonatal Medicine 22(1): 72-75.				
Affiliation/Source of funds				
Department of Obstetrics and Gynecology, Shahid Sedughi Hospital, Shahid Sedughi University of Medical Sciences and Health Services, Yazd, Iran. Not supported by a pharmaceutical company.				
Study design	Level of evidence		Location/setting	
RCT	II		Hospital (single-centre)	
Intervention		Comparator		
Tranexamic acid: 1 g/10 mL IV slowly infused over 5 minutes, 10 minutes prior to incision.		Placebo – 5% glucose dextrose solution (same regimen as TXA)		
Population characteristics				
Women at full-term with their first pregnancy. Mean age ~27 years.				
Length of follow-up		Outcomes measured		
Hospitalisation period		Blood loss, haematology, vital signs, thrombosis.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Pseudorandomised based on odd/even numbers.	Statistical methods not described.	Open-label	Objective measurements of volume and weight used for post-partum haemorrhage so should not be subject to bias.	All patients included in analysis.
Overall quality assessment (descriptive)				
Poor. Pseudo-randomisation using odd/even numbers (not very secure), open-label.				
RESULTS				
Outcome	Intervention group N=45	Comparator group N=45	Statistical significance	
Tranexamic acid (IV)				
	Mean ± SD	Mean ± SD	P value	
Blood loss up to 2 hours postoperative (mL)	28.0 ± 5.5	37.1 ± 9.0	<0.001	
	n/N (%)	n/N (%)	P value	
Thrombosis	0/45 (0)	0/45 (0)	NA	
	Mean ± SD	Mean ± SD	P value	
Postoperative haemoglobin (g/dL)	12.6 ± 1.3	11.7 ± 1.1	<0.01	
Change in haemoglobin from preoperative to postoperative (g/dL)	-0.1 ± 0.6	-2.5 ± 0.8	<0.001	
Clinical importance			Clinical relevance	
Tranexamic acid (IV)				
Blood loss	*Up to 2 hr post-op* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)		1: Patient-relevant clinical outcome.	
Thrombosis	*Thrombosis* No events in either treatment arm.		1: Patient-relevant clinical outcome.	
Haemoglobin	*Pre- to postoperative haemoglobin* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)		2: Predictive surrogate outcome.	
EXTERNAL VALIDITY				

Generalisability
Study conducted specifically in women undergoing caesarean section so likely to be generalisable only to this select group of patients.
Applicability
Study conducted in a single centre in Iran so may not be completely applicable to the Australian/New Zealand setting.
Comments

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; NA, not applicable; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Taghaddomi RJ, Mirzaee A, Attar AS et al (2009) Tranexamic acid reduces blood loss in off-pump coronary artery bypass surgery. Journal of Cardiothoracic and Vascular Anaesthesia 23(3): 312-315.				
Affiliation/Source of funds				
Departments of Anesthesiology and Haematology, Ghaem Hospital, Mashhad University of Medical Sciences, Mashad, Iran; Department of Cardiosurgery, Chaem Hospital, Mashad University of Medial Sciences, Mashad, Iran. Funding not stated.				
Study design	Level of evidence	Location/setting		
RCT	II	Hospital (single-centre)		
Intervention	Comparator			
Tranexamic acid: 1 g given 20 minutes prior to skin incision and 400 mg/h during the entire surgical procedure.	Placebo – saline solution (same regimen as TXA)			
Population characteristics				
Patients scheduled for off-pump CABG. Mean age ~ 62, female 28%, weight 75 kg. No statistically difference in any demographic or perioperative variables between treatment arms.				
Length of follow-up	Outcomes measured			
Hospitalisation period	Blood loss, transfusion, haematology, morbidity.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Random allocation using envelopes. Independent anaesthesiologist prepared coded infusions; not directly involved in clinical treatment of randomised patients.	Assessed by staff not aware of treatment assignment.	Double-blind. Operating room staff and ICU staff unaware of treatment assignment.	Double-blind so treatment/measurement bias should not be an issue.	108 patients enrolled; 8 not analysed (7.4%; 4 converted to on-pump surgery and 4 required re-exploration).
Overall quality assessment (descriptive)				
Fair. Randomised, double-blind, not all patients included in analysis.				
RESULTS				
Outcome	Intervention group N=50	Comparator group N=50	Statistical significance	
Tranexamic acid (IV)				
	n/N (%)	n/N (%)	P value	
Patients transfused with pRBCs (intraoperative)	0/50 (0)	3/50 (6.0)	0.24 *(post-hoc)*	
Patients transfused with pRBCs (0-4 hrs)	0/50 (0)	15/50 (30.0)	<0.001 *(post-hoc)*	
Patients transfused with pRBCs (4-24 hrs)	8/50 (16.0)	9/50 (18.0)	1.00 *(post-hoc)*	
Patients transfused with FFP (0-4 hrs)	2/50 (4.0)	2/50 (4.0)	1.00 *(post-hoc)*	
Patients transfused with FFP (4-24 hrs)	0/50 (0)	0/50 (0)	NA *(post-hoc)*	
Total number of transfused patients	8/50 (16.0)	27/50 (54.0)	<0.001 *(post-hoc)*	
	Mean	Mean	P value	
Intraoperative pRBC transfusion (units per transfused patients)	0	1	0.36	

Postoperative pRBC transfusion 0-4 hrs (units per transfused patients)	0	1.3	<0.001
Postoperative pRBC transfusion 4-24 hrs (units per transfused patients)	1	1	0.5
Postoperative FFP transfusion 0-4 hrs (units per transfused patients)	3	2.5	0.8
Postoperative FFP transfusion 4-24 hrs (units per transfused patients)	0	0	1.00
Total transfusion (units per transfused patients)	1	1.1	NR
	Mean ± SD	Mean ± SD	P value
Intraoperative bleeding (mL)	467 ± 170	531 ± 164	0.62
Postoperative bleeding (0-4 hrs; mL)	87 ± 62	210 ± 195	0.005
Postoperative bleeding (4-24 hrs; mL)	462 ± 118	570 ± 184	0.07
Total bleeding within 24 hrs (mL)	471 ± 182	844 ± 363	<0.001
	n/N (%)	n/N (%)	P value
Myocardial infarction	0/50 (0)	0/50 (0)	NA
Myocardial ischaemia	0/50 (0)	0/50 (0)	NA
Thrombosis	0/50 (0)	0/50 (0)	NA
Neurologic dysfunction	0/50 (0)	0/50 (0)	NA
	Mean ± SD	Mean ± SD	P value
24-hr postoperative haemoglobin (g/dL)	11.2 ± 0.96	11.1 ± 1.2	0.96

Clinical importance	Clinical relevance
Tranexamic acid (IV)	
Transfusion incidence *Intraoperative pRBC transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative 0-4 hrs pRBC transfusion* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) *Postoperative 4-24 hrs pRBC transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative 0-4 hrs FFP transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative 4-24 hrs FFP transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Total number transfused patients* 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.

Transfusion volume	*Intraoperative RBC* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect Postoperative RBC (0-4 hr) 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001) Postoperative RBC (4-24 hr) 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect Postoperative FFP (0-4 hr) 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect Postoperative FFP (4-24 hr) 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect Total transfusion 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Blood loss	*Intraoperative blood loss* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Blood loss up to 0-4 hr postoperative (mL)* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.005) *Blood loss up to 4-24 hr postoperative (mL)* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect Total bleeding within 24 hr 1: Clinically important *benefit*, confidence limit does not include null value (p<0.001)	1: Patient-relevant clinical outcome.
Myocardial infarction	*In-hospital myocardial infarction* No episode of MI reported in either treatment arm	1: Patient-relevant clinical outcome.
Myocardial ischaemia	*In-hospital myocardial ischaemia* No episode of myocardial ischaemia reported in either treatment arm	1: Patient-relevant clinical outcome.
Thrombosis	*In-hospital thrombosis* No episode of thrombosis reported in either treatment arm	1: Patient-relevant clinical outcome.
Neurologic dysfunction	*In-hospital neurologic dysfunction* No episode of neurologic dysfunction reported in either treatment arm	1: Patient-relevant clinical outcome.
Haemoglobin	*24-hr postoperative haemoglobin* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
EXTERNAL VALIDITY		
Generalisability		

Study conducted specifically in patients undergoing off-pump CABG so likely to be generalisable only to this select group of patients.
Applicability
Study conducted in a single centre in Iran so may not be completely applicable to the Australian/New Zealand setting.
Comments

Note: All post-hoc calculations performed using GraphPad software.
Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; MI, myocardial infarction; NA, not applicable; NR, not reported; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

STUDY DETAILS				
Citation				
Wong J, El Beheiry H, Rampersaud YR et al (2008) Tranexamic acid reduces perioperative blood loss in adult patients having spinal fusion surgery. Anesth Analg 107: 1479-1486.				
Affiliation/Source of funds				
Departments of Anaesthesia and Orthopaedics, Toronto Western Hospital, University Health Network, Toronto, Canada; Department of Orthopaedics, St Michael's Hospital, Toronto, Canada; Departments of Anaesthesia and Orthopaedics, Trillium Hospital, Mississauga, Canada. Funded by the Physicians' Services Incorporated Foundation, Toronto, Canada.				
Study design	Level of evidence		Location/setting	
RCT	II		Hospital (3 centres)	
Intervention		Comparator		
Tranexamic acid: bolus 10 mg/kg after induction followed by a maintenance infusion of 1 mg/kg/hr. Note: all patients at one of the three centres received DVT prophylaxis.		Placebo – saline solution (same regimen as TXA) Note: all patients at one of the three centres received DVT prophylaxis.		
Population characteristics				
Adult patients (≥ 18 years) undergoing elective posterior thoracic/lumbar instrumented spinal fusions. Age 57 years TXA and 50 years placebo (p=0.011)[a], female 68%, weight ~73 kg. No differences in any other baseline demographics or patient or surgical factors.				
Length of follow-up		Outcomes measured		
Up to 3 months for thrombosis assessment.		Primary: total estimated and calculated perioperative blood loss (intraoperative and 24 h postoperative). Secondary: transfusion incidence and volume (RMCs, coagulation components), haemoglobin, hospital stay, thrombosis.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Computer-generated random numbers; stratified by surgeon and number of vertebrae fused. Patient assignment placed into sealed envelopes. Independent pharmacist prepared infusions which were identical in appearance.	Assessed by staff not aware of treatment assignment. Standard statistical tests used. Also performed linear and logistic regression.	Double-blind. Research personnel, anaesthesiologists, surgeons and operating room staff blinded to treatment assignment.	Double-blind so treatment/measurement bias should not be an issue.	151 patients enrolled; 4 (2.6%) withdrawn due to excessive and initially uncontrollable surgical bleeding as per a priori exclusion criteria.
Overall quality assessment (descriptive)				
Good. Randomised, double-blind, majority of patients included in analysis (missing patients not likely to bias results.				
RESULTS				
Outcome	Intervention group N=73	Comparator group N=74	Statistical significance	
Tranexamic acid (IV)				
4. Transfusion incidence				
	n/N (%)	n/N (%)	P value	
Perioperative				
Patients transfused with pRBCs	23/73 (31)	30/74 (40)	0.25	
Patients transfused with AWB	24/73 (32)	27/74 (36)	0.65	

Patients transfused with cell-saver blood	33/73 (45)	47/74 (63)	0.026
Patients transfused with FFP	5/73 (7)	9/74 (12)	0.27
Patients transfused with platelets	2/73 (3)	2/74 (3)	0.99
Intraoperative			
Patients transfused with pRBCs	14/73 (19)	17/74 (23)	0.57
Patients transfused with AWB	18/73 (25)	21/74 (28)	0.61
Patients transfused with cell-saver blood	33/73 (45)	46/74 (62)	0.039
Patients transfused with FFP	4/73 (5)	7/74 (9)	0.36
Patients transfused with platelets	2/73 (3)	2/74 (3)	0.99
Postoperative			
Patients transfused with pRBCs	11/73 (15)	21/74 (28)	0.051
Patients transfused with AWB	10/73 (13)	10/74 (13)	0.97
Patients transfused with cell-saver blood	2/73 (3)	3/74 (4)	0.66
Patients transfused with FFP	0/73 (0)	0/74 (0)	NA
Patients transfused with platelets	0/73 (0)	0/74 (0)	NA
5. Transfusion volume			
	Mean ± SD	Mean ± SD	P value
Perioperative			
Patients transfused with pRBCs (mL)	266 ± 541	406 ± 649	0.16
Patients transfused with AWB (mL)	222 ± 343	315 ± 672	0.30
Patients transfused with cell-saver blood (mL)	218 ± 347	334 ± 450	0.083
Intraoperative			
Patients transfused with pRBCs (mL)	169 ± 486	208 ± 436	0.61
Patients transfused with AWB (mL)	150 ± 278	249 ± 656	0.24
Patients transfused with cell-saver blood (mL)	210 ± 343	323 ± 443	0.086
Postoperative			
Patients transfused with pRBCs (mL)	97 ± 239	198 ± 384	0.057
Patients transfused with AWB (mL)	72 ± 200	66 ± 198.2	0.85
Patients transfused with cell-saver blood (mL)	8 ± 49	11 ± 64	0.73
6. Blood loss			
	Mean ± SD	Mean ± SD	P value
Perioperative			
Estimated blood loss (mL)	1592 ± 1315	2138 ± 1607	0.026
Calculated blood loss (mL)	3079 ± 2558	4363 ± 3030	0.017
Calculated RBC loss (mL)	1078 ± 895	1527 ± 1060	0.017
Intraoperative			
Estimated blood loss (mL)	1203 ± 1060	1600 ± 1301	0.044
Postoperative			
Estimated blood loss (mL)	536 ± 471	737 ± 524	0.039
7. Myocardial infarction			

	n/N (%)	n/N (%)	P value
Myocardial infarction	1/73 (0)[b]	0/74 (0)	NS
8. Thrombosis			
	n/N (%)	n/N (%)	P value
Thrombosis	0/73 (0)	1/74 (0)	NS
9. Hospital length of stay			
	Mean ± SD	Mean ± SD	P value
Hospital length of stay (days)	9.19 ± 5.48	8.47 ± 4.12	0.38
10. Haemoglobin			
	Mean ± SD	Mean ± SD	P value
Lowest postoperative haemoglobin (g/dL)	9.4 ± 1.4	8.9 ± 1.3	0.033
Percentage decrease from preoperative to lowest postoperative haemoglobin (%)	31.1 ± 14.2	34.5 ± 13.7	0.154

Clinical importance		Clinical relevance
Tranexamic acid (IV)		
Transfusion incidence	*Perioperative RBC transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Perioperative AWB transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Perioperative cell-saver transfusion* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.026) *Perioperative FFP transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Perioperative platelet transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative RBC transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative AWB transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative cell-saver transfusion* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.039) *Intraoperative FFP transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative platelet transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative RBC transfusion*	1: Patient-relevant clinical outcome.

	4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect (p=0.051) *Postoperative AWB transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative cell-saver transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative FFP transfusion* No postoperative FFP transfusion in either treatment arm *Postoperative platelet transfusion* No postoperative platelet transfusion in either treatment arm	
Transfusion volume	*Perioperative RBC transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Perioperative AWB transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Perioperative cell-saver transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect (p=0.083) *Perioperative FFP transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Perioperative platelet transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative RBC transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative AWB transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative cell-saver transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect (p=0.086) *Intraoperative FFP transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Intraoperative platelet transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.

	Postoperative RBC transfusion 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect (p=0.057) *Postoperative AWB transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative cell-saver transfusion* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect *Postoperative FFP transfusion* No postoperative FFP transfusion in either treatment arm *Postoperative platelet transfusion* No postoperative platelet transfusion in either treatment arm	
Blood loss	*Perioperative estimated blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.026) *Perioperative calculated blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.017) *Perioperative calculated RBC loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.017) *Intraoperative estimated blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.044) *Postoperative estimated blood loss* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.039)	1: Patient-relevant clinical outcome.
Myocardial infarction	*In-hospital myocardial infarction* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Thrombosis	*DVT* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	1: Patient-relevant clinical outcome.
Length of hospital stay	*Length of hospital stay* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
Haemoglobin	*Lowest postoperative haemoglobin* 1: Clinically important *benefit*, confidence limit does not include null value (p=0.033) *Percentage reduction from baseline of lowest postoperative haemoglobin* 4: Range of estimates includes clinically important effects, but also compatible with no or harmful effect	2: Predictive surrogate outcome.
EXTERNAL VALIDITY		
Generalisability		
Study conducted specifically in adult patients undergoing spinal fusion surgery so likely to be generalisable only to this select group of patients.		

Applicability
Study conducted in three Canadian centres so likely to be applicable to the Australian/New Zealand setting.
Comments
Multiple linear regression found TXA to be significantly related to reduced perioperative blood loss (Mean difference -580 mL (95% CI: -949, -211; p=0.002) while logistic regression found a trend for TXA to be related to reduced incidence of perioperative allogeneic pRBC transfusion (OR 0.43; 95% CI: 0.17, 1.07); p=0.068). Authors note the study not powered to find a reduction in incidence or volume of transfusion.

Note: All post-hoc calculations performed using GraphPad software.

Abbreviations: AWB, autologous white blood; DVT, deep vein thrombosis; FFP, fresh frozen plasma; ITT, intention-to-treat; IV, intravenous; NA, not applicable; OR, odds-ratio; pRBCs, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid.

[a] Regression analysis showed age not significantly associated with blood loss or transfusion requirements.

[b] Asymptomatic MI only; diagnosed via elevation of cardiac enzymes.

Intervention 9 – Appropriate patient positioning

Level II evidence

Citation				
De Sio M, Autorino R, Quarto G, Calabro F, Damiano R, Giugliano F, Mordente S, D'Armiento M. Modified Supine versus Prone Position in Percutaneous Nephrolithotomy for Renal Stones Treatable with a Single Percutaneous Access: A Prospective Randomized Trial. European Urology 2008;54(1):196-203.				
Affiliation/Source of funds				
Seconda Universita degli Studi, Naples, Italy. University of Cassino, Cassino, Italy. Universita Magna Graecia, Catanzaro, Italy. Funding: NR				
Study design		Level of evidence		Location/setting
RCT		Level II		Medical institutions
Intervention		Comparator		
Modified supine position		Prone position		
Population characteristics				
75 patients undergoing nephrolithotomy.				
Length of follow-up		Outcomes measured		
Until discharge		Blood loss, hospital stay, surgery duration, postoperative complications.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Computer generated numbers	No difference in preoperative characteristics between patient groups.	Not possible for surgeons to be blinded of intervention.	Analyst unaware of treatment allocation,	Analysed based on ITT
Overall quality assessment (descriptive)				
Good. This study was well described and with appropriate statistical and subgroup analysis conducted.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Change in Haemoglobin (g/dL)	–2.3 (-3.5, -0.4)	–2.2 (-3.3, -0.5)	0.23
Mean hospital stay (days)	4.3 (Range: 2.2–8.4)	4.1 (Range: 2.4–7.8)	0.18
Operating room time (minutes)	43 (25–120)	68 (55–140)	<0.001
Major complications (loss of nephrostomy tract, fever)	1/39 patients	0/36 patients	0.2
Minor complications (transient fever, renal colic, significant bleeding)	7 patients	5 patients	0.16

Outcome	Clinical importance	Clinical relevance
Change in Haemoglobin	4	1
Mean hospital stay	4	2
Operating room time	1	2
Major complications	4	1
Minor complications	4	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted in patients undergoing nephrolithotomy. As such, generalisability is likely limited to patients undergoing such a procedure, with similar clinical characteristics.		
Applicability		
This study was conducted in Italy, where the healthcare system is likely comparable to Australia.		
Comments		
This study showed that the supine position was similar to the prone position for percutaneous stone removal.		

Abbreviations: NR, not reported; RCT, randomised clinical trial.

Citation				
Ko MT, Chuang KC, Su CY. Multiple analyses of factors related to intraoperative blood loss and the role of reverse Trendelenburg position in endoscopic sinus surgery. Laryngoscope 2008;118(9):1687-1691.				
Affiliation/Source of funds				
Chang Gung Memorial Hospital, Kaohsiung Medical Centre, Chang Gung University College of Medicine, Kaohsiung, Taiwan. Funding: NR				
Study design		Level of evidence		Location/setting
RCT		Level II		Hospital
Intervention		Comparator		
Reverse Trendelenburg position		Supine position		
Population characteristics				
60 patients undergoing Endoscopic sinus surgeries.				
Length of follow-up		Outcomes measured		
NR		Blood loss, surgery duration		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Method NR	No difference in preoperative characteristics between patient groups.	Not possible for surgeons to be blinded of intervention.	All operations performed by same surgeon.	No loss to follow-up
Overall quality assessment (descriptive)				
Fair. This study was well described and utilised appropriate statistical tests.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Total blood loss (mL)	126 (SD: 85.8)	251.67 (SD: 139.1)	P<0.001
Blood loss per minute	0.87 (SD: 0.6)	1.74 (SD:1.0)	P<0.001
Surgery duration (minute)	138.5 (SD: 50.8)	165.5 (SD: 56.1)	P=0.056
Outcome	Clinical importance	Clinical relevance	
Total blood loss	2: reduced blood loss, however difference may not be clinically significant	1	
Blood loss per minute	2: reduced blood loss, however difference may not be clinically significant	1	
Surgery duration	4	2	

EXTERNAL VALIDITY
Generalisability
This RCT was conducted in patients undergoing Endoscopic sinus surgery. As such, generalisability is likely limited to patients undergoing such a procedure, with similar clinical characteristics.
Applicability
This study was conducted in Taiwan, while differences may exist, the level and quality of healthcare is likely comparable to Australia. As such the findings should be applicable.
Comments
This study showed that RTP may reduce intraoperative blood loss.

Abbreviations: NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Ong SM, Taylor GJSC. Can knee position save blood following total knee replacement? Knee 2003;10(1):81-85.				
Affiliation/Source of funds				
University Hospital of Leicester NHS Trust, Glenfield Hospital, UK. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Intervention 1: Leg elevated 35° at the hip with knee flexed to 70° for 6 hours post-operation Intervention 2: Leg elevated 35° at the hip with knee extended	Knee extended and level with bed after operation			
Population characteristics				
60 (20 in each treatment group) patients undergoing primary unilateral total knee replacement for osteoarthritis.				
Length of follow-up	Outcomes measured			
Until discharge	Haemoglobin loss, blood transfusion requirements, morbidity.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Using sealed envelopes	No difference in preoperative characteristics between patient groups.	Envelopes with treatment allocation only opened after operation.	NR	No loss to follow-up
Overall quality assessment (descriptive)				
Fair. This study was well described and utilised appropriate statistical tests.				

RESULTS				
Outcome	Intervention group 1	Intervention group 2	Comparator group	Statistical significance
Haemoglobin loss (g/dL)	3.8 (95%CI 3.3, 4.3)	3.6 (95%CI 3.0, 4.2)	4.8 (95%CI 4.0, 5.6)	P=0.018
Blood transfusion (median number of units transfused)	0 (Range 0, 2)	0 (Range 0,2)	2 (Range 0, 3.5)	P=0.3
Blood transfusion incidence	7/20 patients	7/20 patients	11/20 patients	P=0.3
Knee swelling (cm)	3.4 (Range 1.0, 7.0)	3.3 (Range 1.5, 8.0)	3.8 (Range 1.5, 8.0)	P=0.6
Incidence of DVT	1/20 patients	1/20 patients	0/20 patients	NR
Outcome	Clinical importance		Clinical relevance	
Haemoglobin loss	2: reduced haemoglobin loss, difference may not be clinically significant		1	

Blood transfusion (median number of units transfused)	4	1
Blood transfusion incidence	4	1
Knee swelling (cm)	4	2
Incidence of DVT	NR	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted in patients undergoing total knee replacement. As such, generalisability is likely limited to patients undergoing such a procedure, with similar clinical characteristics.		
Applicability		
This study was conducted in the UK, where the health system is similar to that in Australia. As such, findings are likely applicable.		
Comments		
This study recommends the elevation of the leg at 35° from the hip with knee extended following total knee replacement for more favourable patient outcomes.		

Abbreviations: NR, not reported; RCT, randomised clinical trial.

Citation				
Pace A, Yousef A. The effect of patient position on blood loss in primary cemented total hip arthroplasty. Archives of Orthopaedic and Trauma Surgery 2008;128(10):1209-1212.				
Affiliation/Source of funds				
Queens Medical Centre, Derby Road, Nottingham, UK. Funding: NR				
Study design	Level of evidence	Location/setting		
RCT	Level II	Hospital		
Intervention	Comparator			
Lateral position	Supine position			
Population characteristics				
101 patients undergoing hip arthroplasty				
Length of follow-up	Outcomes measured			
NR, at least up to five days post-operation	Blood loss, change in haemoglobin, transfusion requirements, wound infection, deep vein thrombosis.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Using sealed envelopes opened before surgery	No difference in preoperative characteristics between patient groups.	Not possible to blind surgeon from patients' treatment group.	Standardised transfusion protocol use for both groups.	No loss to follow-up
Overall quality assessment (descriptive)				
Fair. This study was well described and utilised appropriate statistical tests.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Total blood loss (mL)	1129 (95%CI 989, 1310)	1156 (95%CI 954, 1265)	P=0.41
Surgery duration (minute)	74 (95%CI 63, 89)	69 (95%CI 55, 79)	P=0.31
Transfusion incidence	5/51 patients	8/50 patients	P=0.65
Transfusion rate (units/patient)	0.39	0.32	P=0.56
Change in haemoglobin (g/dL) 1 day after operation 5 days after operation	 3.6 (95%CI 2.9, 5.0) 3.7 (95%CI 2.6, 5.1)	 3.9 (95%CI 2.5, 4.6) 3.75 (95%CI 2.4, 4.9)	 P=0.24 P=0.92
Wound infection	0/51 patients	2/50 patients	NS
Deep vein thrombosis	1/51 patients	0/50 patients	NS

Outcome	Clinical importance	Clinical relevance
Total blood loss	4	1
Surgery duration	4	2
Transfusion requirement	4	1

Transfusion rate	4	1
Change in haemoglobin	4	1
Wound infection	4	1
Deep vein thrombosis	4	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted in patients undergoing spinal surgery. As such, generalisability is likely limited to patients undergoing such a procedure, with similar clinical characteristics.		
Applicability		
This study was conducted in the UK where the level and quality of healthcare is likely comparable to Australia. As such the findings should be applicable.		
Comments		
This study shows that patient positioning in supine or lateral during hip arthroplasty surgery has no bearing on the amount of blood loss.		

Abbreviations: CI, confidence interval; NR, not reported; NS, not statistically significant; cRCT, randomised clinical trial.

Citation				
Park CK. The effect of patient positioning on intraabdominal pressure and blood loss in spinal surgery. Anesthesia and Analgesia 2000;91(3):552-557.				
Affiliation/Source of funds				
Eulji University School of Medicine, Taejon, Korea. Funding: NR				
Study design		Level of evidence		Location/setting
RCT		Level II		Hospital
Intervention		Comparator		
Narrow pad width of Wilson spinal supporting frame		Wide pad width of Wilson spinal supporting frame		
Population characteristics				
40 ASA I and II patients undergoing posterior lumbar spinal surgery.				
Length of follow-up		Outcomes measured		
NR		Blood loss, blood transfusion dose and frequency, surgery duration, change in haemoglobin levels.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised. Method NR	No difference in preoperative characteristics between patient groups.	Double-blinded. Surgical team blinded to treatment group	All operations performed by same surgeon, and same anaesthesiologist. Standardised transfusion protocol use for both groups.	No loss to follow-up
Overall quality assessment (descriptive)				
Good. This study was well described and utilised appropriate statistical tests.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Total blood loss (mL)	878 (SD: 521)	436 (SD: 159)	P<0.05
Blood loss per vertebra (mL)	381 (SD: 236)	190 (SD: 65)	P<0.05
Surgery duration (minute)	136.8 (SD:23.7)	134.0 (SD: 27.8)	NS
Transfusion frequency	5 patients	1 patient	NS
Transfusion dose per patient	2.2 units	2 units	NS
Haemoglobin (g/dL) Preoperative Postoperative	 13.1 (SD: 1.0) 10.6 (SD: 1.1)	 13.1 (SD: 1.4) 11.3 (SD: 1.1)	NS
Outcome	Clinical importance	Clinical relevance	
Total blood loss	2: increased blood loss, may not be clinically significant	1	

Blood loss per vertebra	2: increased blood loss, may not be clinically significant	1
Surgery duration	4	2
Transfusion frequency	4	1
Transfusion dose per patient	4	1
Change in haemoglobin	4	1
EXTERNAL VALIDITY		
Generalisability		
This RCT was conducted in ASA I and II patients undergoing spinal surgery. As such, generalisability is likely limited to patients undergoing such a procedure, with similar clinical characteristics.		
Applicability		
This study was conducted in Korea, while differences may exist, the level and quality of healthcare is likely comparable to Australia. As such the findings should be applicable.		
Comments		
This study shows that the use of wide pad on the Wilson frame decreases blood loss.		

Abbreviations: NR, not reported; NS, not statistically significant; RCT, randomised clinical trial; SD, standard deviation.

Citation				
Widman J, Isacson J. Lateral position reduces blood loss in hip replacement surgery: A prospective randomized study of 74 patients. International Orthopaedics 2001;25(4):226-227.				
Affiliation/Source of funds				
St Gorans Hospital, Stockholm, Sweden. Funding: NR				
Study design		Level of evidence		Location/setting
RCT		Level II		Hospital
Intervention		Comparator		
Lateral position		Supine position		
Population characteristics				
74 patients undergoing hip replacement surgery				
Length of follow-up		Outcomes measured		
NR		Blood loss, surgery duration, blood transfusion frequency and dose.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/ measurement bias	Follow-up (ITT)
Randomised, using a table of random numbers	Uneven gender distribution between groups	Not possible for the surgeon to be blinded to the treatment group of the patient.	Dropouts from study were random. The surgeons and surgical technique were the same in the two groups.	Drop-outs not included in analysis.
Overall quality assessment (descriptive)				
Fair.				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Intraoperative blood loss (mL)	508 (SD:316)	723 (SD: 316)	P<0.001 (Gender adjusted)
Blood loss after 24 hours (mL)	1273 (SD:407)	1374 (SD: 458)	P=0.043 (Gender adjusted)
Blood transfusion frequency	17/30 patients	30/44 patients	P=0.336
Blood transfusion volume (mL)	321 (SD: 341)	407 (SD: 362)	P=0.307
Surgery duration (minutes)	70 (SD: 11)	77 (SD: 19)	NR

Outcome	Clinical importance	Clinical relevance
Intraoperative blood loss	2: difference may not be clinically significant	1
Blood loss after 24 hours	2: difference may not be clinically significant	1
Blood transfusion frequency	4	1
Blood transfusion volume	4	1
Surgery duration	NR	2

EXTERNAL VALIDITY
Generalisability
This RCT was conducted in patients undergoing hip replacement surgery. As such, generalisability is likely limited to patients undergoing such a procedure, with similar clinical characteristics.
Applicability
This study was conducted in the Sweden, where the level of healthcare is likely comparable to that in Australia. As such, findings are likely applicable.
Comments
Patients operated in the lateral position had significantly lower total blood loss (~201mL less)

Abbreviations: NR, not reported; RCT, randomised clinical trial; SD, standard deviation.

Intervention 10 – Preoperative autologous donation

Level I evidence

Citation		
Carless P, Moxey A, O'Connell D, and Henry D. (2004) Autologous transfusion techniques: A systematic review of their efficacy. Transfusion Medicine 14:123-144.		
Affiliation/Source of funds		
Research supported by a grant obtained from the National Health and Medical Research Council of Australia and a special purpose grant from the Hunter Area Pathology Service, Australia		
Study design	Level of evidence	Location/setting
Systematic review of RCTs and observational studies with meta-analysis Search conducted July 2002	I	NA

Intervention	Comparator
Autologous transfusion techniques: preoperative Autologous blood deposit (PAD), ANH, and cell salvage (CS). NOTE: This form only contains RCT info relevant for PAD. Sample size (PAD) N=566	Comparator: No Autologous transfusion technique (active versus active comparisons were excluded) Sample size (control for PAD) N=553
Population characteristics	
Patients older than 18 years undergoing any type of surgery. Four trials involved curative surgery for colorectal cancer, three involved orthopaedic surgery, and one trial involved liver surgery.	
Length of follow-up	Outcomes measured
NA	Mortality, re-operation, infection, wound complication, thrombosis, non-fatal MI, rate of allogeneic red blood cell transfusion, and volume of allogeneic blood transfused

INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Concealment of treatment allocation and the method of randomisation were judged to be inadequate in all trials (kappa=1.0 for each of these quality items)	The trials studied an equal ratio of males to females. The mean (or median) age of the participants studied ranged from 57.5 to 71 years for those randomised to PAD and 60.5 to 71 years for those patients randomised to control. SR did not discuss the variability of other baseline characteristics between intervention groups.	Blinding was not reported in any trial.	Non detected	NR
Overall quality assessment (descriptive)				
Good				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Number of subjects transfused with allogeneic blood 8 trials (N=1119; 566 PAD, 553 control)			RR (95% CI): 0.37 (0.26, 0.54) P<0.05 (P*het*=0.0018)	
Number of subjects transfused with allogeneic blood (cancer surgery) 5 trials (N=NR)			RR (95% CI): 0.49 (0.38, 0.63) P<0.05 (P*het*=NR)	
Number of subjects transfused with allogeneic blood (orthopaedic surgery) 3 trials (N=NR)			RR (95% CI): 0.16 (0.07, 0.36) P<0.05 (P*het*=NR)	
Number of subjects transfused with allogeneic blood (transfusion protocol) 5 trials (N=NR)			RR (95% CI): 0.49 (0.37, 0.63) P<0.05 (P*het*=NR)	
Number of subjects transfused with allogeneic blood (no transfusion protocol) 3 trials (N=NR)			RR (95% CI):0.15 (0.06, 0.37) P<0.05 (P*het*=NR)	

Number of subjects receiving any allogeneic and/or autologous RBC transfusion 7 trials (N=1088; 550 PAD, 538 control)			RR (95% CI): 1.29 (1.12, 1.48) P<0.05 (P*het*=0.0049)
Preoperative haemoglobin concentration			On average, the preoperative Haemoglobin level of patients who deposited their blood was 1.23 gdL^{-1} (95% CI: 0.71, 1.74 gdL^{-1})
Mortality			Insufficient evidence
Morbidity: infection 3 tirals (N=NR)			RR (95% CI): 0.70 (0.34, 1.43) P>0.05 (P*het*=NR)
Morbidity: thrombosis 2 trials (N=NR)			RR (95% CI): 0.82 (0.21, 3.13) P>0.05 (P*het*=NR)
Morbidity: other			Insufficient evidence for stroke, DVT, and pulmonary embolus.
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population			
Applicability			
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).			
Comments			
The search found eight RCTs for PAD with a total of 1119 subjects.			

Citation				
Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, and McCollum C. (2006) Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model (Provisional abstract). Health Technology Assessment 10:1-228.				
Affiliation/Source of funds				
One of the authors received sponsorships from Haemonetics and AstraTech to attend conferences. The author has also given invited lectures for AstraTech Ltd and Unomedical with honoraria and expenses paid.				
Study design	Level of evidence		Location/setting	
Systematic review of reviews and a systematic update of Henry 2001.	1		NA	
Intervention		Comparator		
Transfusion strategies to minimise perioperative allogeneic blood transfusion: cell salvage, PAD, PAD plus EPO, EPO, ANH, cell salvage plus ANH, AFs, FSs, restrictive transfusion thresholds or protocols. NOTE: this form only contains information relevant for PAD. Search conducted January 2004		Control group that did not receive PAD.		
Population characteristics				
For inclusion, the SRs had to only include adults undergoing elective, non-urgent surgery. Of the three studies included in the update, one study was performed in patients undergoing maxillofacial surgery, and two were carried out on patients undergoing joint arthroplasty (one for total hip arthroplasty and the other for a mixuture of of unilateral, bilateral, primary and revision hip and knee arthroplasty.				
Length of follow-up		Outcomes measured		
NA		Number of patients transfused with allogeneic blood, volume of allogeneic blood transfused, number of patients transfused with autologous blood, volume of autologous blood transfused, preoperative Hb, volume of autologous blood wasted and length of hospital stay.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
All of the studies in the update were randomised but only one of the studies described an adequate method to secure allocation concealment.		Blinding was unclear in all three studies, but in one study only the operating surgeon was blinded only to whether the patient had received EPO and the participants received open-label treatment.	Two of the studies in the systematic update reported using a transfusion protocol.	One study did not perform an ITT analysis as participants were excluded from the analysis by the authors and in one study it was unclear whether an ITT analysis had been used. One study did analyse all participants who were recruited.

Overall quality assessment (descriptive)			
Good			
RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Number of patients transfused with allogeneic blood (all studies) 11 trials (N=1423)	149/716 (21%)	375/707 (53%)	RR (95% CI): 0.36 (0.25, 0.51) P<0.05 (P*het*=0.0005)
Number of patients transfused with allogeneic blood (transfusion protocol) 7 trials (N=1196)	138/ 585 (24%)	299/611 (49%)	RR (95% CI): 0.48 (0.38, 0.60) P<0.05 (P*het*=0.18)
Number of patients transfused with allogeneic blood (no transfusion protocol) 4 trials (N=217)	11/121 (9%)	76/96 (79%)	RR (95% CI): 0.12 (0.04, 0.33) P<0.05 (P*het*=0.08)
Number of patients transfused with allogeneic blood (orthopaedic surgery) 5 trials (N=425)	21/221 (10%)	75/204 (37%)	RR (95% CI): 0.21 (0.11, 0.43) P<0.05 (P*het*=0.07)
Number of patients transfused with allogeneic blood (oncology) 5 trials (N=950)	128/467 (27%)	280/483 (58%)	RR (95% CI): 0.49 (0.38, 0.63) P<0.05 (P*het*=0.15)
Number of patients transfused with allogeneic blood (maxillofacial surgery) 1 trial (N=48)	0/28 (0%)	20/20 (100%)	RR (95% CI): 0.02 (0.00, 0.28) P<0.05 (P*het*=NA)
Number of patients transfused with allogeneic/autologous blood (all studies) 9 trials (N=1232)	496/620 (80%)	343/612 (56%)	RR (95% CI): 1.33 (1.10, 1.61) P<0.05 (P*het*<0.00001)
Number of patients transfused with allogeneic/autologous blood (transfusion protocol) 5 trials (N=1015)	384/499 (77%)	267/516 (52%)	RR (95% CI): 1.48 (1.16, 1.89) P<0.05 (P*het*=0.001)
Number of patients transfused with allogeneic/autologous blood (no transfusion protocol) 4 trials (N=217)	112/121 (93%)	76/96 (79%)	RR (95% CI): 1.10 (0.95, 1.29) P>0.05 (P*het*=0.26)
Number of patients transfused with allogeneic/autologous blood (orthopaedic surgery) 3 trials (N=234)	105/125 (84%)	43/109 (39%)	RR (95% CI): 1.78 (0.61, 5.20) P>0.05 (P*het*<0.00001)

Number of patients transfused with allogeneic/autologous blood (oncology) 5 trials (N=950)	363/467 (78%)	280/483 (58%)	RR (95% CI): 1.38 (1.20, 1.58) P<0.05 (P*het*=0.13)
Any thrombosis 3 trials (N=250)	6/140 (4%)	3/110 (3%)	RR (95% CI): 0.82 (0.21, 3.13) P>0.05 (P*het*=0.53)
Any infection 3 trials (N=621)	74/309 (24%)	81/312 (26%)	RR (95% CI): 0.70 (0.34, 1.43) P>0.05 (P*het*=0.07)
Preoperative Hb levels (g/dl) 5 trials (N=534)	N=267	N=267	WMD (95% CI): -1.16 (-1.60, -0.73) P<0.05 (P*het*=0.004)
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population.			
Applicability			
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).			
Comments			
Three new RCTs were included in the update of the Henry 2001 PAD systematic review			

Abbreviations: AvC, active versus control

Citation				
Duffy G and Neal KR. (1996) Differences in postoperative infection rates between patients receiving autologous and allogeneic blood transfusion: a meta-analysis of published randomized and nonrandomized studies (Structured abstract). Transfusion Medicine 6:325-328.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR of RCTs and retrospective studies Date of search NR	I	NA		
Intervention	Comparator			
Autologous transfusion (including PAD or cell salvage)	Allogeneic blood transfusion only			
Population characteristics				
Patients undergoing any surgical operation.				
Length of follow-up	Outcomes measured			
	Infections			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
NR	Baseline characteristics NR	NR	SR did not define whether a transfusion protocol was used	NR
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Infections 1 trial (N=77)	4/44 (9%)	13/33 (39%)	OR (95% CI): 6.5 (2.1, 20.7) P<0.05 (P*het*=NA)	
Clinical importance	Clinical relevance			
EXTERNAL VALIDITY				
Generalisability				
Limited generalisability (due to uncertainty regarding the small sample size, and lack of info regarding potential sources of bias)				
Applicability				
The results are applicable to the Australian context (the study was conducted in Germany)				
Comments				
NB: only one RCT of PAD was included (Heiss 1993)				

Citation				
Forgie MA, Wells PS, Laupacis A, and Fergusson D. (1998) Preoperative autologous donation decreases allogeneic transfusion but increases exposure to all red blood cell transfusion: Results of a meta-analysis. Archives of Internal Medicine 158:610-616.				
Affiliation/Source of funds				
Dr Laupacis is the recipient of the First Fellowship from the International Society of Technology Assessment in Health Care, funded by the PPP Medical Trust, United Kingdom. Investigators of the International Study of Perioperative Transfusion (ISPOT) received funding from the following sources. The Ottawa Coordinating Centre: Janssen Ortho Inc, Don Mills, Canada; investigators from Australia: the National Health and Medical Research Council and the Hunter Area Pathology Services, Newcastle; investigators from France: Haemonetics France, Ortho Diagnostics France, and University Victor Segalen, Bordeaux; investigators from Scotland: the Scottish National Blood Transfusion Service and the Clinical Resources and Audit Group of the Scottish Health Service; and investigators from the United States: Baxter Healthcare Corporation Biotech Group, Deefield, Ill, and the Emory Center for Clinical Evaluation Scieinces, Atlanta, Ga.				
Study design	Level of evidence	Location/setting		
SR of RCTs and observational studies Search conducted April 1996	I	NA		
Intervention	Comparator			
PAD (defined as the process by which patients donate blood prior to elective surgery and subsequently receive their own blood in the perioperative period if transfusion is required.	Not PAD			
Population characteristics				
Patients undergoing elective surgery. In two of the trials the patients underwent hip arthroplasty, in three of the trials the patients underwent colon resection, and in one trial the patients underwent liver resection.				
Length of follow-up	Outcomes measured			
NR	Number of patients exposed to allogeneic blood; total number of patients who underwent transfusion with RBCs (including both allogeneic and autologous units); postoperative complications			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
	One of the trials had a large difference in the male-female ratio between control and PAD groups (5:10/8:8). Another trial did not report the male-female ratio. With the exception of one trial that did not report the mean age for the control group, the mean ages in the trials were balanced between the intervention groups.	All 6 randomised studies scored 2 on the Jadad quality scale. Since it is ethically inappropriate to blind autologous donors to the treatment they received, the maximum possible score for quality in these studies was 3.	Two of the trials did not report a transfusion protocol.	Two of the trials had patient withdrawals as follows (control/PAD): 0/14 and 5/26.

Overall quality assessment (descriptive)			
Good			
RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Patients transfused with allogeneic blood 6 trials (N=1099; 613 PAD, 486 control)	NR	NR	OR (95% CI): 0.17 (0.08, 0.32) P<0.05 (P*het*<0.008)
Patients transfused with allogeneic blood (colorectal surgery) 3 trials (N=977; 542 PAD, 435 control)	NR	NR	OR (95% CI): 0.26 (0.19, 0.37) P<0.05 (P*het*>0.26)
Patients transfused with allogeneic blood (THA) 2 trials (N=91; 61 PAD, 30 control)	NR	NR	OR (95% CI): 0.20 (0.00, 0.28) P<0.05 (P*het*>0.03)
Patients transfused with allogeneic blood (transfusion protocol) 4 trials (N=1008; 558 PAD, 450 control)	NR	NR	OR (95% CI): 0.25 (0.17, 0.37) P<0.05 (P*het*>0.20)
Patients transfused with allogeneic blood (no transfusion protocol) 2 trials (N=91; 55 PAD, 36 control)	NR	NR	OR (95% CI): 0.02 (0.00, 0.24) P<0.05 (P*het*>0.10)
Patients transferred with allogeneic and/or autologous blood 5 trials (N=1068; 597 PAD, 471 control)	NR	NR	OR (95% CI): 3.03 (1.70, 5.39)
Postoperative infection (colorectal surgery) 2 trials (N=595; 297 PAD, 298 control)	NR	NR	OR (95% CI): 1.44 (0.49, 4.26) P>0.05 (P*het*=NR)
Other morbidity	NR	NR	Insufficient evidence for MI, angina, venous thrombosis, and prolonged hospital admission
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
This review is generalisable to elective surgery with moderate blood loss.			
Applicability			
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).			

Comments
6 RCTs were included.

Abbreviations: THA, total hip arthroplasty

Citation			
Gurusamy KS, Li J, Sharma D, and Davidson BR. (2009) Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. Gurusamy. Kurinchi. Selvan. , Li Jun, Sharma. Dinesh. , Davidson. Brian. R. Cardiopulmonary interventions to decrease. blood loss. and blood transfusion requirements. for liver resection. Cochrane Database of Systematic Reviews: Reviews 2009. Issue. 4 John. Wiley. & So.			
Affiliation/Source of funds			
None declared			
Study design	Level of evidence	Location/setting	
SR Search conducted November 2008	I	NA	
Intervention	Comparator		
Any cardiopulmonary intervention aimed at reducing operative blood loss or perioperative allogeneic blood transfusion requirements	Control: no intervention, placebo, or another intervention aimed at reducing surgical blood loss or at decreasing allogeneic blood transfusion requirements during surgery.		
Population characteristics			
Patients undergoing liver resection.			
Length of follow-up	Outcomes measured		
NA	Perioperative mortality, survival, liver failure, perioperative morbidity (other than mortality and liver failure), transfusion requirements, operating time, hospital stay, ICU stay, transaction blood loss, operative blood loss, blood loss within 24 hours.		
INTERNAL VALIDITY			
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
See Hashimoto 2007 below	See Hashimoto 2007 below	See Hashimoto 2007 below	See Hashimoto 2007 below	See Hashimoto 2007 below
Overall quality assessment (descriptive)			
Good			
RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Mortality	0/40	0/39	0 (0, 0) P=NA (P*het*=NA)
Morbidity: bile leak	0/40 (0%)	1/39 (3%)	RR (95% CI): 0.33 (0.01, 7.75) P=0.49 (P*het*=NA)
Morbidity: intra-abdominal bleeding	0/40 (0%)	1/39 (3%)	RR (95% CI): 0.33 (0.01, 7.75) P=0.49 (P*het*=NA)
Number requiring allogeneic blood transfusion	0/40 (0%)	0/39 (0%)	RR (95% CI): 0 (0, 0) P=NA (P*het*=NA)

Transection blood loss (mL)	140 (185)	230 (185)	WMD (95% CI): -90.0 (-171.60, -8.40) P=0.031 (P*het*=NA)
Operative blood loss (mL)	403 (144)	440 (144)	WMD (9%% CI): -37.0 (-100.51, 26.51) P=0.25 (P*het*=NA)
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
See Hashimoto 2007 below			
Applicability			
See Hashimoto 2007 below			
Comments			
SR found one trial assessing PAD (Hashimoto 2007)			

Citation				
Henry DA, Carless PA, Moxey AJ, O'Connell D, Forgie MA, Wells P, and Fergusson DA. (2001) Preoperative autologous donation for minimising perioperative allogeneic blood transfusion. Cochrane Database of Systematic Reviews				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR of RCT January 2004	I	The included trials were conducted in Germany (N=3), Greece (N=1), Japan (N=1), Sweden (N=3), the Netherlands (N=2), and the USA (N=2).		
Intervention	Comparator			
PAD	Any			
Population characteristics				
Adult patients undergoing elective or non-urgent surgery. Six trials involved orthopaedic surgery, four involved curative surgery for colorectal cancer, one involved liver surgery and one trial involved maxillofacial surgery.				
Length of follow-up	Outcomes measured			
NA	Proportion of patients who were transfused with allogeneic blood or any blood transfusion (allogeneic or autologous); amounts of allogeneic and autologous blood transfused; adverse transfusion reactions; preoperative morbidity; preoperative haemoglobin levels; reported postoperative complications; and mortality.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Using the Cochrane grading system for allocation concealment, two trials were assessed as providing inadequate allocation concealment, and, in eight trials the allocation concealment was not clearly described. One trial was assessed to have adequate allocation concealment.		Blinding was not reported in any of the trials assessed for methodological quality.	Eight of the trials reported the use of transfusion protocols (with a transfusion 'trigger')	Of the trials assessed for methodological quality, seven trials reported either no exclusions or reported the use of ITT analysis. In one trial, exclusions were reported; however, these were deemed unlikely to cause bias. In one trial, exclusions were deemed excessive and likely to cause bias
Overall quality assessment (descriptive)				
Good				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Patients transfused with allogeneic blood[1] 11 trials (N=1423)	149/716 (21%)	375/707 (53%)	RR (95% CI): 0.36 (0.25, 0.51) RD (95% CI): -0.44 (-0.61, -0.27) NNT (95% CI): 2.3 (1.6, 3.7) P<0.05 (P*het*=0.00052)
Patients transfused with allogeneic blood (oncology) 5 trials (N=950)	128/467 (27%)	280/483 (58%)	RR (95% CI): 0.49 (0.38, 0.63) P<0.05 (P*het*=0.15)
Patients transfused with allogeneic blood (orthopaedic surgery) 5 trials (N=425)	21/221 (10%)	75/204 (37%)	RR (95% CI): 0.21 (0.11, 0.43) P<0.05 (P*het*=0.07)
Patients transfused with allogeneic blood (maxillofacial surgery) 1 trial (N=48)	0/28 (0%)	20/20 (100%)	RR (95% CI): 0.02 (0.00, 0.28) P<0.05 (P*het*=NA)
Patients transfused with allogeneic blood (transfusion protocol) 7 trials (N=1206)	138/595 (23%)	299/611 (49%)	RR (95% CI): 0.48 (0.38, 0.60) P<0.05 (P*het*=0.18)
Patients transfused with allogeneic blood (no transfusion protocol) 4 trials (N=217)	11/121 (9%)	76/96 (79%)	RR (95% CI): 0.12 (0.04, 0.33) P<0.05 (P*het*=0.08)
Patients transfused with allogeneic and/or autologous blood 9 trials (N=1232)	496/620 (80%)	343/612 (56%)	RR (95% CI): 1.33 (1.10, 1.61) P<0.05 (P*het*<0.000001)
Patients transfused with allogeneic and/or autologous blood (orthopaedic surgery) 3 trials (N=234)	105/125 (84%)	43/109 (39%)	RR (95% CI): 1.78 (0.61, 5.20) P>0.05 (P*het*<0.00001)
Patients transfused with allogeneic and/or autologous blood (oncology) 5 trials (N=950)	363/467 (78%)	260/483 (54%)	RR (95% CI): 1.38 (1.20, 1.58) P<0.05 (P*het*=0.13)
Patients transfused with allogeneic and/or autologous blood (maxillofacial surgery) 1 trial (N=48)	28/28 (100%)	20/20 (100%)	RR (95% CI): 0 (0, 0) (P*het*=NA)

Patients transfused with allogeneic and/or autologous blood (transfusion protocol) 5 trials (N=1015)	384/499 (77%)	267/516 (52%)	RR (95% CI): 1.48 (1.16, 1.89) P<0.05 (P*het*=0.001)
Patients transfused with allogeneic and/or autologous blood (no transfusion protocol) 4 trials (N=217)	112/121 (93%)	76/96 (79%)	RR (95%CI): 1.10 (0.95, 1.29) P>0.05 (P*het*<0.00001)
Preoperative haemoglobin, g/dL 5 trials (N=534; 267 PAD, 267 control))	Mean (SD):	-	WMD (95% CI): -1.16 (-1.60, -0.73) P< 0.05 (P*het*=0.004)
Infection 3 trials (N=621)	74/309 (24%)	81/312 (26%)	RR (95% CI): 0.70 (0.34, 1.43) P>0.05 (P*het*=0.07)
Any thrombosis 3 trials (N=250)	6/140 (4%)	3/110 (3%)	RR (95% CI): 0.82 (0.21, 3.13) P>0.05 (P*het*=0.53)
Other morbidity/mortality			There were insufficient data to draw any conclusions about the effect of PAD on mortality, stroke, DVP, and pulmonary embolus.
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
Patients considered similar to guideline target population			
Applicability			
All the studies included in this review were conducted in countries with well developed healthcare systems (not specifically Aus/NZ).			
Comments			
Twelve studies were included in the analysis. Lorenz 1991 was not assessed for methodological quality, however, as only an English abstract was available.			

[1]Of the 761 patients randomised to PAD, the majority (N=467) donated their blood prior to cancer surgery.

Citation				
Laupacis A and Fergusson D. (1998) The efficacy of technologies to minimise perioperative allogeneic transfusion (Structured abstract). Kluwer. Academic Publishers.17-36.				
Affiliation/Source of funds				
NR				
Study design	Level of evidence	Location/setting		
SR January 1997	I	NA		
Intervention	Comparator			
Technologies to minimise perioperative allogeneic transfusion: aprotinin, desmopressin, tranexamic acid, epsilon aminocaproic acid, erythropoietin, PAD, ANH. NB: this form only reports results for PAD	Any			
Population characteristics				
Adult patients undergoing elective surgery. Types of surgery included cardiac, colorectal, liver resection and orthopaedic surgery.				
Length of follow-up	Outcomes measured			
NR	Proportion of patients receiving at least one unit of allogeneic packed red blood cells, perioperative MI, re-operations because of bleeding.			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
NR	Baseline characteristics NR	NR	Use of transfusion protocol included in subgroup analysis.	NR
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Proportion of patients receiving allogeneic transfusion 6 trials (N=933)	N=NR	N=NR	OR (95% CI): 0.17 (0.08, 0.32) P<0.05 (P*het*=NR)	
Proportion of patients receiving allogeneic transfusion (colorectal surgery) Number of trials NR (N=NR)	–	–	OR (95% CI): 0.26 (0.19, 0.37) P<0.05 (P*het*=NR)	

Proportion of patients receiving allogeneic transfusion (THA) Number of trials NR (N=NR)	–	–	OR (95% CI): 0.20 (0.00, 0.28) P<0.05 (P*het*=NR)
Proportion of patients receiving allogeneic transfusion (transfusion protocol) Number of trials NR (N=NR)	–	–	OR (95% CI): 0.25 (0.17, 0.37) P<0.05 (P*het*=NR)
Proportion of patients receiving allogeneic transfusion (no transfusion protocol) Number of trials NR (N=NR)	–	–	OR (95% CI): 0.02 (0.00, 0.24) P<0.05 (P*het*=NR)
Proportion of patients receiving allogeneic and/or autologous transfusion 5 trials (N=NR)	–	–	OR (95% CI): 3.03 (1.70, 5.39) P<0.05 (P*het*=NR)
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The SR is generalisable for elective, non urgent surgery.			
Applicability			
The studies were mostly from countries with similar health-care systems to Australia			
Comments			

Citation				
Vamvakas EC. (2002) Meta-analysis of randomized controlled trials comparing the risk of postoperative infection between recipients of allogeneic and autologous blood transfusion. Vox Sanguinis 83:339-346.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence	Location/setting		
SR January 2002	I	NA		
Intervention	Comparator			
Autologous transfusion: PAD, ANH, perioperative cell salvage. NB: this form only summarises the results of PAD. Vamvakas is not discussed in I1-4, because the meta-analyses conflate results from trials testing ANH alone with trials testing cell salvage alone.	Transfusion of non-WBC reduced allogeneic RBCs or whole blood.			
Population characteristics				
Patients undergoing any surgical operation				
Length of follow-up	Outcomes measured			
NA	Postoperative infection			
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Not reported			Use of transfusion protocol not reported	
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Outcome	Intervention group	Comparator group	Statistical significance	
Rate of infection 2 trials (N=590)	NR	NR	OR (95% CI): 1.35 (0.45, 4.08) P>0.05 (P*het*=NR)	
Clinical importance	Clinical relevance			
EXTERNAL VALIDITY				
Generalisability				
The populations in the trials are similar to the guideline population.				
Applicability				
The systematic review is applicable to the Australian context.				

Comments
NB: five studies met the criteria for the meta-analysis.

Level II evidence

Citation				
Bouchard D, Marcheix B, Al Shamary S, Vanden Eynden F, Demers P, Robitaille D, Pellerin M, Perrault LP, and Carrier M. (2008) Preoperative autologous blood donation reduces the need for allogeneic blood products: A prospective randomized study. Canadian Journal of Surgery 51:422-427.				
Affiliation/Source of funds				
None declared				
Study design	Level of evidence		Location/setting	
RCT	II		Canada / hospital	
Intervention		Comparator		
PAD: protocol consisted of harvesting 2 units of 350 mL each (or 6 mL/kg when the patient's weight was below 60 kg). 1 unit was harvested weekly. N=25		Control: allogeneic blood only. N=23		
Population characteristics				
Patients undergoing elective cardiac surgery.				
Length of follow-up		Outcomes measured		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
It is unclear whether allocation was blinded from those responsible for recruiting subjects.	The treatments arms had similar demographic characteristics	Neither the patient nor the surgeon was blinded to the group assignment; however, the ICU intensivist, nurses and residents were blinded.	A transfusion protocol was used.	All analyses were conducted ITT. PAD was not completed in 2 patients (8%) because of worsened angina pectoris.
Overall quality assessment (descriptive)				
Fair				
RESULTS				

Outcome	Intervention group	Comparator group	Statistical significance
Mean (SD) perioperative blood loss, mL	416 (190)	450 (281)	P=0.62
Mean (SD) postoperative blood loss, mL	936 (583)	909.5 (576)	P=0.88
Mean (SD) duration of surgery, min	174.7 (44.9)	177.6 (62.3)	P=0.85
Patients transfused with autologous blood	6/25 (24%)	-	-
Mean (SD) units of autologous blood transfused (for those transfused)	2 (1.2)	-	-

Patients transfused with allogeneic blood products	4/25 (16%)	9/23 (39%)	RR=2.25 P=0.036
Patients transfused with allogeneic blood	0	7/23 (30%)	-
Mean (SD) units of allogeneic whole blood transfused (for those transfused)	0	2 (1.2)	-
Patients transfused with FFP	1/25 (4%)	5/23 (22%)	P=0.06
Mean (SD) units of FFP transfused (for those transfused)	4	2.8 (1)	NR
Patients transfused with platelets	3/25 (12%)	4/23 (17%)	P=0.59
Mean (SD) units of platelets transfused (for those transfused)	4.3 (2.9)	6 (0)	NR
Patients transfused with cryoprecipitate	0	1/23 (4%)	P=0.29
Mean (SD) units of cryoprecipitate transfused (for those transfused)	-	10	NR
Patients transfused with allogeneic and/or autologous blood products	11/25 (44%)	9/23 (39%)	P=0.036
Mean (SD) preoperative haemoglobin concentration, g/L	128.7 (14.4)	135.0 (12.9)	P=0.12
Mean (SD) haemoglobin concentration 24 hours after surgery, g/L	81.6 (12.1)	86.2 (13)	P=0.22
Mean (SD) haemoglobin concentration 5 d after surgery, g/L	102.8 (11.8)	107.7 (11.9)	P=0.16
Mean (SD) preoperative prothrombin time, sec	9.7 (2.8)	9.4 (1.1)	P=0.69
Mean (SD) prothrombin time 30 min after surgery, sec	13.2 (3.9)	13.5 (2.2)	P=0.76
Mean (SD) prothrombin time 24 h after surgery, sec	10.3 (1.3)	10.9 (1.7)	P=0.16
Mean (SD) preoperative fibrinogen concentration, g/L	4.3 (1.5)	3.1 (0.9)	P=0.004
Mean (SD) fibrinogen concentration 30 min after surgery, g/L	3.0 (0.9)	2.6 (0.7)	P=0.10
Mean (SD) fibrinogen concentration 24 h after surgery, g/L	6.2 (1.3)	5.1 (1.2)	P=0.006
Length of stay in hospital, d	5.4 (0.9)	5.4 (0.9)	P=1.00

Length of stay in ICU, d	1.5 (0.6)	1.5 (0.6)	P=1.00
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The patients investigated are similar to the guideline population.			
Applicability			
The study was conducted in Montreal; however, the results are applicable to the Australian context.			
Comments			

[1]The 1 patient received 2 autologous blood units.
[2]1 patient received 3 allogeneic blood units, and another patient received 6 platelet units.
[3]1 patient received 4 FFP units and 3 patients received platelets (mean 4.3, SD 2.9 units).
[4]5 patients received FFP units (mean 2.8, SD 1 units), 4 patients received 6 platelet units and 1 patient received 10 cryoprecipitate units.

Citation				
Hashimoto T, Kokudo N, Orii R, Seyama Y, Sano K, Imamura H, Sugawara Y, Hasegawa K, and Makuuchi M. (2007) Intraoperative blood salvage during liver resection: A randomized controlled trial. Annals of Surgery 245:686-691.				
Affiliation/Source of funds				
Study supported by a grant from the Kanae Foundation for Life and Socio-medical Science, a grant from the Public Trust Surgery Research Fund, a grant from the Japanese Clinical Oncology Fund, a grant from the Public Trust Haraguchi Memorial Cancer Research Fund in Japan, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.				
Study design	Level of evidence		Location/setting	
RCT	II		Japan / hospital	
Intervention		Comparator		
PAD: blood volume equal to approximately 0.7% of the patient's body weight was collected before the liver transection. The collected blood was reinfused into the patient after the graft procurement. N=40		Control: "control group using a minimization method" N=39		
Population characteristics				
Patients scheduled to undergo liver graft procurement.				
Length of follow-up		Outcomes measured		
NR		The primary outcome measure was blood loss during hepatic parenchymal division. Secondary outcome measures consisted of total blood loss, blood loss during hepatic parenchymal division per unit transaction area, CVP at the start of the hepatic parenchyma division, serum aspartate aminotransferase and total bilirubin levels on the third postoperative day, length of hospital stay, and morbidity.		
INTERNAL VALIDITY				
Allocation	Results	Blinding analysis	Treatment/measurement bias	Follow-up (ITT)
Participants were randomised to treatment; however, it is unclear whether allocation was concealed to those in charge of recruiting participants.	The treatment arms were similar in baseline and operative values.	The patients and surgeons were blinded to randomisation results.	None detected	One patient in the control group was excluded from analysis after randomisation because the operation was stopped due to an asthmatic attack.
Overall quality assessment (descriptive)				
Fair				

RESULTS			
Outcome	Intervention group	Comparator group	Statistical significance
Morbidity[1]	Major: 1/40 Minor: 6/40	Major: 2/39 Minor: 9/39	P>0.999
Median (range) length of hospital stay	14 (10 to 36)	14 (11 to 46)	P=0.476
Median (range) preoperative haemoglobin concentration, g/dL	13.0 (11.0 to 15.7)	13.6 (11.6 to 15.9)	P=0.455
Median (range) haemoglobin concentration 24-h postoperative, g/dL	12.3 (9.6 to 15.9)	12.5 (10.5 to 15.0)	P=0.280
Median (range) preoperative PT-INR	1.11 (0.95 to 1.34)	1.10 (0.91 to 1.31)	P=0.350
Median (range) PT-INR 24 h postoperative	1.76 (1.30 to 2.37)	1.77 (1.29 to 2.32)	P=0.456
Median (range) intraoperative blood loss	Total, mL: 403 (120 to 1240) During liver parenchymal division, mL: 140 (40 to 430) During liver parenchymal division per unit transactional area (mL/cm^2): 2.15 (0.86 to 7.37)	Total, mL: 440 (130 to 1230) During liver parenchymal division, mL: 230 (40 to 660) During liver parenchymal division per unit transactional area (mL/cm^2): 3.75 (0.64 to 7.93)	P-value Total: 0.257 During liver parenchymal division: 0.034 During liver parenchymal division per unit transactional area (mL/cm^2): 0.012
Mean (range) total operation time (min)	473 (385 to 640)	470 (380 to 730)	P=0.883
Clinical importance		Clinical relevance	
EXTERNAL VALIDITY			
Generalisability			
The study population is limited to people undergoing liver graft procurement, however it is still somewhat generalisable to other elective surgeries associated with moderate blood loss.			
Applicability			
The study was conducted in Japan, which may limit it's applicability to the Australian context.			
Comments			

[1]Complications requiring surgical or other interventions were defined as major complications, while those that resolved with conservative treatment but prolonged the hospital stay by more than 2 weeks (eg, wound infection, ileus, and minor bile leakage) were defined as minor complications.
Abbreviations: PT-INR, prothrombin time international normalisation ratio