Technical report

Volume 3 – Appendix E

Prepared for

National Blood Authority

Project

Update of Patient Blood Management Guideline for Adults with Critical Bleeding

The Commonwealth of Australia

as represented by the National Blood Authority

[redacted]

prepared by

HTANALYSTS Pty Ltd

February 2023

Note

This volume presents the data extraction forms (Appendix E) that outline the characteristics of reviews and studies included in the systematic literature review on Patient Blood Management in people with critical bleeding. Volume 1 presents the methods and main body of evidence and Volume 2 presents Appendix A (literature search results) through to Appendix D (critical appraisal or risk of bias forms). These three volumes cover all research questions developed for this topic.

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Appendix E Data extraction forms

E1 Prognostic factors (Question 1)

Systematic reviews/meta-analyses

STUDY DETAILS: Razzaghi 2012			
Citation			
Razzaghi, A., & Barkun, A. N. (2012). Platelet transfusion threshold in patients with upper gastrointestinal bleeding: A systematic review. *Journal of Clinical Gastroenterology*, 46(6), 482-486. doi:10.1097/MCG.0b013e31823d33e3			
Affiliation/Source of funds			
Details on funding or potential conflicts of interest not provided.			
Study design	**Level of evidence**	**Location**	**Setting**
Narrative SR of RCTs, observational studies and case-series	I-III	NR	Surgery (nonvariceal upper GI bleeding)
Prognostic Factor		**Comparator**	
Platelet transfusion		NA	
Population characteristics			
Patients with thrombocytopenia in the setting of nonvariceal upper GI bleeding. Patient populations varied between studies, including patients with leukemia, bone marrow transplant, hematopoietic progenitor cell transplant, and gynaecologic cancer.			
Length of follow-up		**Outcomes measured**	
OVID, MEDLINE, EMBASE, CENTRAL, and ISI Web of knowledge 4.0 were searched for Citations between January 1950 and February 2011.		Transfusion volume	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. Insufficient reporting of search strategy, no list of excluded studies with justification, no risk of bias conducted, no meta-analysis was performed, and funding source or potential conflict of interest was not reported. *Risk of bias for included studies:* Risk of bias for included studies was not conducted by the review authors.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**Results (narrative)**		***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
Platelet count			
Transfusion Volume N = NR (10 studies) Gmur 1991 Fanning 1995 GilFernandez 1996 Rebulla 1997 Heckman 1997 Wandt 1998 Lawrence 2001 Navarro 1998	- Eight studies recommended a platelet count of 10×10^9/L as an appropriate threshold. - One study (gynaecologic cancer patients) recommended a threshold of 5×10^9/L (Fanning 1995). - One study (Gmur 1991) recommended a transfusion threshold of 5-20×10^9/L in leukemia patients, depending on the clinical		NR

STUDY DETAILS: Razzaghi 2012		
Zumberg 2002 Dietrich 2005	context, with most haemorrhagic events occurring at platelet counts of 10×10^9/L or greater. - Target platelet count in those with active haemorrhage is 50×10^9/L, however in some clinical settings should be up to 100×10^9/L.	

EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
The evidence is not directly generalisable to the Australian population, and it is hard to judge whether it is sensible to apply. Limited evidence is given regarding the populations of included studies. Some studies include prophylactic platelet transfusion, which is not relevant to the target population.
Applicability (relevance of the evidence to the Australian health care system)
The evidence is not applicable to the Australian healthcare context. Studies included in the review are published prior to 2005. It is unclear if these studies accurately represent current practice or consensus, and therefore applicability of the evidence to the Australian health care system is unknown.
Additional comments
Authors conclusions: In conclusion, the review found there was lack of directly applicable, high quality study results that were able to inform optimal therapeutic platelet count transfusion volumes in patients with acute upper GI bleeding. The SR found no studies that assessed patients with upper GI haemorrhage, and therefore generalised findings from haematology and oncology patients. A target platelet count of between 50×10^9/L and 100×10^9/L has been suggested depending on the clinical setting. Most studies recommended a platelet count of 10×10^9/L as trigger for transfusion. Lack of quality studies highlights the need for quality RCT evidence to address the clinical question more precisely. *List of relevant included studies:* Gmur 1991, Fanning 1995, GilFernandez 1996, Rebulla 1997, Heckman 1997, Wandt 1998, Lawrence 2001, Navarro 1998, Zumberg 2002, Dietrich 2005

CI, confidence interval; GI, gastrointestinal; ITT, intention-to-treat; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SR, systematic review

Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Pacagnella 2013			
Citation			
Pacagnella 2013 Pacagnella, R. C., Souza, J. P., Durocher, J., Perel, P., Blum, J., Winikoff, B., & Gulmezoglu, A. M. (2013). A Systematic Review of the Relationship between Blood Loss and Clinical Signs. PLoS ONE, 8 (3) (no pagination)(e57594). doi:http://dx.doi.org/10.1371/journal.pone.0057594			
Affiliation/Source of funds			
The study was funded by Gynuity Health Projects and the World Health Organization Author affiliations: The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of observational studies	I-III	USA, Japan	Obstetrics (using general trauma as a proxy)
Prognostic factor		**Comparator**	
SBP, SI, HR		N/A	
Population characteristics			
Patients with haemorrhage			
Length of follow-up		**Outcomes measured**	
Medline, EMBASE, Lilacs, Scielo, ISI and Google Scholar were searched in February 2012.		Blood loss [b] Mortality	
INTERNAL VALIDITY			

STUDY DETAILS: Pacagnella 2013				
Overall risk of bias (descriptive)				
Rating: Serious Description: More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. Review provided insufficient detail on included studies, did not provide list of excluded studies, and did not account for study risk of bias when attempting to interpret results. Included studies: The STROBE checklist to assess risk of bias. Nine (of 30) studies were considered of high quality. 21 studies did not describe or provide sufficient detail of the study population, the health status of the population or the inclusion criteria. Most studies did not provide information regarding the method of assessment of clinical signs.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Statistical analysis**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
SBP				
Mortality N = 19,759 (4 studies) Bruns 2008 Cancio 2008 Edelman 2007 Vandromme 2010	Due to inconsistencies in study design and limited reporting of data a qualitative analysis was conducted. All studies found an association between low SBP and mortality.		NR	*NR*
Blood loss[b] N = 28,442 (6 studies) Brasel 2007 Chen 2007 Hagiwara 2010 Vandromme 2010 Vandromme 2011b Zarzaur 2008	six studies assessed the relationship between SI and blood loss. The studies found an association between SI and blood loss.		AUC NR 0.71 NR 0.6 0.79 0.71	NR
SI				
Mortality N = 16,077 (1 study) Zarzaur 2008	One study assessed the relationship between SI and mortality. The study found an association between SI and mortality.		NR	NR
Blood loss[b] N = 16,830 (3 studies) Chen 2007 Hagiwara 2010 Zarzaur 2008	Three studies assessed the relationship between SI and blood loss. The studies found an association between SI and blood loss.		AUC 0.77 NR 0.78	NR
HR				
Blood loss[b] N = 28,169 (5 studies)	Five studies assessed the relationship between HR and blood loss. The studies found an association between HR and blood loss		AUC	NR

STUDY DETAILS: Pacagnella 2013			
Brasel 2007 Chen 2007 Hagiwara 2010 Vandromme 2011b Zarzaur 2008		0.56-0.59 0.66 NR 0.65 0.73	
Mortality N = 16, 077 1 study	One study assessed the relationship between HR and mortality. The study found an association between HR and mortality	NR	NR
EXTERNAL VALIDITY			
Generalisability (relevance of the study population to the Guidelines target population)			
The evidence is not directly generalisable to the Australian population, and it is hard to judge whether it is sensible to apply. The study attempts to generalise general trauma data to the obstetric setting, however there are significant differences between trauma and obstetric populations that make this generalisation incorrect, as identified in the study.			
Applicability (relevance of the evidence to the Australian health care system)			
The evidence is not applicable to the Australian healthcare context. Included studies are conducted in the USA and Japan, studies that met inclusion criteria were indirect measurements that used proxies to estimate blood loss. The study did not provide sufficient details of included studies to accurately validate applicability to the Australian health care context.			
Additional comments			
Authors conclusions: The review found a substantial variability in the relationship between blood loss and clinical signs, making it very difficult to establish specific cut-off points for clinical signs that could be used as triggers of clinical interventions. However, the shock index was found to be an accurate indicator of compensatory changes in the cardiovascular system due to blood loss. Included studies: Vandromme 2011b, Hagiwara 2010, Vandromme 2010, Bruns 2008, Cancio 2008, Chen 2007, Chen 2008, McLaughlin 2009, Zarzaur 2008, Brasel 2007, Edelman 2007			

AUC, area under the curve; CI, confidence interval; HR, heart rate; ITT, intention-to-treat; MD, mean difference; N/A., not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SBP, systolic blood pressure; SI, shock index; STROBE. Strengthening the Reporting of Observational studies in Epidemiology

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%. b Blood loss is defined as the amount of blood loss that requires triggering of clinical intervention in the management of post-partum haemorrhage.

STUDY DETAILS: Abdul-Kadir 2014
Citation
Abdul-Kadir, R., McLintock, C., Ducloy, A. S., El-Refaey, H., England, A., Federici, A. B. et al. Evaluation and management of postpartum hemorrhage: Consensus from an international expert panel. Transfusion. 2014; 54(7): 1756-1768. http://dx.doi.org/10.1111/trf.12550
Affiliation/Source of funds
Author affiliations: Royal Free Hospital, London; Auckland City Hospital; Centre Hospitalier Régional Universitaire de Lille, Lille, France; Chelsea &Westminster Hospital and Imperial College School of Medicine, London; L. Sacco University Hospital, University of Milan, Italy; Duke University School of Medicine, Durham, North Carolina; Coagulation Center Rhine Ruhr Area, Duisburg, Germany; Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; University of Heidelberg, Germany; University of Virginia, Charlottesville, Virginia; The Mary M. Gooley Hemophilia Treatment Center and the Rochester General Hospital, Rochester, New York; Yale University School of Medicine, New Haven, Connecticut; Università degli Studi di Milano and Luigi Villa Foundation, Milan, Italy; University of Montreal, Montréal, Québec, Canada. *Funding and conflict of interests*: The authors received funding support and honoraria from CSL Behring to attend the consensus meeting but report no other conflicts of interest or funding sources.

STUDY DETAILS: Abdul-Kadir 2014			
Study design	**Level of evidence**	**Location**	**Setting**
Expert consensus and SR of observational studies	I-III	NR	Obstetrics
Prognostic factor		**Comparator**	
Platelet count, Haemoglobin level, Temperature, Fibrinogen		Not applicable	
Population characteristics			
PPH			
Length of follow-up		**Outcomes measured**	
Date of systematic search not provided. Consensus meeting was held in November 2011		Blood loss >500mL Requirement of transfusion	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. Review did not provide sufficient detail of included studies, did not perform risk of bias assessment, did not perform a meta-analysis, and did not discuss the heterogeneity of studies. *Risk of bias included studies:* Risk of bias was not reported.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate:** **OR (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
Platelet count				
Blood loss >500mL N = NR (1 study) Al-Zirqi 2008	One study found that low platelet count was associated with greater risk of PPH with blood loss >500mL		1.9 (NR)	*NR*
Haemoglobin level				
Blood loss >500mL N = NR (1 study) Al-Zarqi 2008	One study found that existing anaemia (<9 g/dL haemoglobin) was associated with greater risk of PPH with blood loss >500mL		2.2 (NR)	NR
Temperature				
Blood loss >500mL N = NR (1 study) ROCOG 2017	One study found that a raised body temperature during labour was associated with a greater risk of PPH with blood loss >500mL		2.0 (NR)	NR
Fibrinogen				
Requirement of transfusion N = NR (4 studies) Charbit 2007 Cortet 2012 Peyvandi 2012 Rouse 2006	Three studies assessed the association between PPH requiring transfusion and fibrinogen levels. - Two studies (Charbit 2007, Cortet 2012) reported a lower (≤ 2 g/L) mean plasma fibrinogen level in women who developed more severe PPH. - Peyvandi 2012 was unable to determine if decreased fibrinogen is an independent and measurable predictor of severe PPH or simply a measure of blood loss. - Rouse 2006 notes that low fibrinogen may require transfusion of fibrinogen concentrate, which has been used in obstetrics for the management of PPH since 1948.			
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population, and it is hard to judge whether it is sensible to apply. There is limited information provided on the population of included studies and considering ethnicity, age, and other population-relevant factors affect risk of PPH, it is not possible to accurately judge generalisability of the review.				

STUDY DETAILS: Abdul-Kadir 2014
Applicability (relevance of the evidence to the Australian health care system)
The evidence is probably applicable to the Australian healthcare context with some caveats. The international expert consensus is probably applicable to the Australian health care system however it is difficult to judge due to limited data provided on included studies.
Additional comments
Authors conclusions: The numerous risk factors for PPH necessitate a multidisciplinary management that requires early and regular monitoring of pregnant women. *List of relevant included studies:* Al-Zirqi 2008, Charbit 2007, Combs 1991, Cortet 2012, Pevandi 2012, ROCOG 2017, Rouse 2006

CI, confidence interval; not applicable, not applicable; NR, not reported; OR, odds ratio; PPH, post-partum haemorrhage; SD, standard deviation; SR, systematic review

Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Haas 2015			
Citation			
Haas, T., Fries, D., Tanaka, K. A., Asmis, L., Curry, N. S., & Schochl, H. (2015). Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? British Journal of Anaesthesia, 114(2), 217-224. doi:https://dx.doi.org/10.1093/bja/aeu303			
Affiliation/Source of funds			
Funding: funding was received from CSL Behring to perform literature searches. The authors received no funding support for writing of the manuscript and all writing was performed by the authors. *Author affiliations:* CSL Behring GmbH, Octapharma AG, TEM International, TEM Innovations Fresenius Kabi, and B Braun AG. Austrian National Bank, AOP Orphan, Pfizer, Astra Zeneca, Baxter, Biotest, Fresenius, Glaxo, Haemoscope, Hemogem, Lilly, LFB, Mitsubishi Pharma, NovoNordisk, Octapharm, and Tem International. LFB, Austrian Society for Anesthesiology, Intensive Care and ResusCitation, German Interdisciplinary Society for Intensive Care Medicine (DIVI), European Society of Intensive Care Medicine (ESA) Society for Thrombosis and Haemostasis (GTH), European Society of Intensive Care Medicine (ESICM).			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review	I-III	USA, Australia Hess 2009, USA Mitra 2007, Australia Mannucci 1982, NR Murray 1988, USA Ciavarelli 1987, NR	Trauma (Hess 2009, Ciavarella 1987, Mitra 2007) Surgery (Mannucci 1982)
Prognostic factor		**Comparator**	
INR, PT, aPTT		NA	
Population characteristics			
Patients with critical bleeding (trauma patients admitted to the emergency room)			
Length of follow-up		**Outcomes measured**	
Ovid Medline was searched between 1950 and November 2013		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating {AMSTAR): Critically low *Description: More than one critical flaw with or without non-critical weaknesses* – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. Review did not employ a comprehensive search strategy, did not provide sufficient information on included studies and did not provide a list of excluded studies.			

STUDY DETAILS: Haas 2015				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
INR				
Mortality N = 35441 (2 studies) Hess 2009 Mitra 2007	an INR of ≥ 1.3 was associated with a 6.3-fold increased risk of in-hospital mortality INR is a predictor of mortality with an OR of 1.62 (95% CI: 1.18–2.24, $p < 0.01$)			
PT and aPTT				
Mortality N = 155 (2 Studies) Ciavarella 1987	microvascular bleeding was associated with severe abnormalities of coagulation factor levels, 20% (PT and aPTT values 1.8 times control).			
Mitra 2007	aPTT is a predictor of mortality with an OR of 1.01 (95% CI: 1.01–1.02, $p < 0.01$)			
Transfusion volume N = NR (2 studies) Mannucci 1982	Mannucci 1982 reported a PT > 1.2 times normal or aPTT>1.25 times normal were found in 93% of patients who underwent major surgery and received massive transfusion. However De Backer 2008 concluded PT and aPTT are not useful for guidance of FFP transfusion in severe bleeding.			
Murray 1998	recommended FFP transfusion if PT or aPPT is >1.5 times prolonged during massive transfusion.			
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population but could be sensibly applied. Included studies are referenced from Australian and British management guidelines, however there is insufficient evidence provided to determine if the population can be directly generalised to the Australian population. The inclusion of both perioperative and emergency trauma patients however, the small study population may not accurately represent the general population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. The review includes publications referenced by Australian and British guidelines and therefore is applicable to the Australian health care system. The inclusion of old studies may reduce the applicability of the evidence.				
Additional comments				
Authors conclusions: The authors conclude that there are significant shortcomings of using INR, PT, and aPTT in the management of major bleeding in the perioperative or trauma setting. Current trigger levels are not supported by evidence-based data, Quality of studies is poor. Newer methods such as viscoelastic testing should be used as an alternative as they provide a more comprehensive analysis and provide the results more quickly. *Included studies:* Hess 2009, Mitra 2007, Ciavarella 1987, Mannucci 1982, Murray 1998				

aPTT, activated partial thromboplastin time; CI, confidence interval; INR, international normalised ratio; ITT, intention-to-treat; MD, mean difference; PP, per-protocol; PT. prothrombin time; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Baxter 2016
Citation
Baxter, J., Cranfield, K. R., Clark, G., Harris, T., Bloom, B., & Gray, A. J. (2016). Do lactate levels in the emergency department predict outcome in adult trauma patients? A systematic review. Journal of Trauma and Acute Care Surgery, 81(3), 555-566. doi:http://dx.doi.org/10.1097/TA.0000000000001156
Affiliation/Source of funds
Funding: Details on funding was not provided. The authors declared no conflicts of interest.

STUDY DETAILS: Baxter 2016			
Author affiliations: University of Edinburgh, Edinburgh; St John's Hospital, Livingston; Royal Infirmary of Edinburgh, Edinburgh; Barts Health NHS Trust; Queen Mary University of London, London; Emergency Medicine Research Group Edinburgh (EMeRGE), Edinburgh, United Kingdom.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of cohort studies	I-III	All included studies were from developed countries (e.g. USA)	Trauma/Emergency department
Prognostic factor		**Comparator**	
Lactate		NA	
Population characteristics			
Adult (age>16), trauma patients who had initial lactate measurements taken on arrival to hospital			
Length of follow-up		**Outcomes measured**	
Medline, Embase and CINAHL databases were searched for Citations between 1980 and March 2016. DARE and CDSR were used to search for reference and relevant cited articles.		Mortality Transfusion volume	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. Selection of Study design was not described, and list of excluded studies was not provided. *Risk of bias of included studies:* Reporting of recruitment methods were poor, and it was unclear if there was adequate participation of eligible individuals, with subsequent risk of selection bias. Risk of attrition bias was high in all studies, as the reporting of numbers of participants and those lost to follow-up were universally poor. Risk of bias relating to study confounding was high or moderate in most studies.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**Survivors** **Lactate** **(mmol/L)** **Mean ± SD**	**Non-survivors** **Lactate (mmol/L)** **Mean ± SD**	**Risk estimate** **Adjusted OR (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Lactate				
Mortality N = 34,120 *All trauma* (9 studies)				
Duane 2008	NR	NR		
Initial > 2.2 mmol/L			1.067 (0.887–1.283)	NR
24 hrs > 2.2 mmol/L	NR	NR	1.79 (1.259–2.546)	NR
Dezman 2015	NR	NR	NR	NR
Lavery 2000				
Arterial ≥ 2.0 mmol/L	NR	NR	1.1 (0.978–1.15)	NR
Venous ≥ 2.0 mmol/L	2.5 (1.8)	3.8 (3.0)	1.2 (1.15–1.35)	NR
Mizushima 2011			1.21 (1.15–1.29)	NR
Odom 2012				
< 2.5 mg/dL			1.0 (reference)	< 0.001
2.5–3.9 mg/dL			1.5 (1.1–2.0)	
≥ 4.0 mg/dL			3.8 (2.8–5.3)	
Pal 2006	3.0 (0.04)	5.2 (0.3)	NR	<0.001
Parsikia 2014	2.1 (NR)	3.2 (NR)	1.01 (1.00–1.02)	<0.001
Regnier 2012				
Initial	1.4 (0.4)	1.5 (0.4)	NR	0.77
2hr	1.6 (0.8)	1.7 (0.8)	NR	0.82

STUDY DETAILS: Baxter 2016				
Schmelzer 2008				
Venous	3.4 (2.6)	4.0 (2.9)	NR	0.1999
Arterial	3.4 (2.9)	4.2 (2.9	NR	0.0656
Subsets of trauma patients (14 studies)				
Aslar 2004				
≥ 4 mmol/L	2.64 (1.08)	7.98 (3.8)	10.58 (1.88–59.24)	< 0.001
Baron 2004	3.1 (2.5, 3.7)	6.2 (3.5, 8.8)	NR	0.03
Blow 1990	NR	NR	NR	< 0.05
Callaway 2009				
> 4 mmol/L	2.8 (1.8)	2.0 (1.0)	4.2 (2.4-7.5)	< 0.001
F-Montali 2009	2.9 (2.0)	5.0 (4.9)	NR	0.007
Ipekci 2013	3.3. (1.7)	7.7 (4.2)	NR	< 0.01
Kaplan 2003	3.6 (1.5)	11.1 (3.6)	NR	< 0.001
Mica 2012	3.0 (2.3)	5.6 (3.9)	NR	< 0.001
Nast-Kolb 1997		4.8 (0.8)	NR	< 0.05
without organ failure	3.1 (0.3)			
with organ failure	5.0 (0.6)			
Neville 2011	NR	NR		
>2.5 mmol/L, SBP 90–109			3.7 (1.6–8.2)	NR
>2.5 mmol/L, SBP ≥ 110			4.3 (2.2–44.0)	NR
Oullet	2.2	3.6	NR	< 0.0001
Regnier	NR	NR	NR	NR
Sammour 2008	NR	NR	NR	NR
Vandromme 2010	NR	NR		NR
<2.5 mmol/L			RR 1.0 (reference)	
2.5–5.0 mmol/L			RR 2.4 (1.5–3.7)	
5.1–7.5 mmol/L			RR 3.2 (1.9–5.3)	
>7.5 mmol/L			RR 6.2 (3.7–10.3)	
Transfusion volume N = 1093 (3 studies) Regnier 2012 Baron 2004 Ipekci 2013	In all trauma patients, increased lactate and lactate clearance were found to predict massive haemorrhage, defined as blood transfusion of >6 packed red cell units within 24 hours and/or death from haemorrhagic shock. Increased lactate was also found to be associated with increased blood loss in penetrating torso trauma patients. Two studies found that raised lactate was associated with blood product requirements, but this was not significant in a study which only looked at patients with isolated extremity injuries.			

EXTERNAL VALIDITY

Generalisability (relevance of the study population to the Guidelines target population)

The evidence is directly generalisable to the Australian population with some caveats. Included studies were conducted in general trauma patients within an emergency department setting. Most studies are multi-centre studies and in a large number of participants. The evidence can be sensibly generalised to the target population.

Applicability (relevance of the evidence to the Australian health care system)

The evidence is probably applicable to the Australian healthcare context with some caveats. Location of studies is not provided; however, studies were conducted in developed countries. Most studies had broad inclusion criteria.

Additional comments

Authors conclusions:

The author notes the review demonstrates a clear relationship between lactate levels in injured patients and mortality. There is however, limited evidence to support specific lactate cut-off values. Additionally, there is a clear relationship between increasing lactate levels and injury severity and increased risk of poor outcome. Despite some limitations in the currently available evidence, lactate should be considered as part of the assessment of illness severity in adult trauma patients.

STUDY DETAILS: Baxter 2016
List of relevant included studies:
Baron 2004, Duane 2008, Dezman 2015, Ipekci 2013, Lavery 2000, Mizushima 2011, Odom 2012, Pal 2006, Parsikia 2014, Regnier 2012, Schmelzer 2008, Neville 2011, Vandromme 2010, Calaway 2009, Fuglister 2009, Paladino 2008, Sammour 2008, Mica 2012, Duellet 2012, Baron 2007, Aslar 2004, Kaplan 2003, Blow 1990

CDSR, Cochrane Database of Systematic Reviews; CI, confidence interval; CINAHL, Cumulative index to nursing and allied health literature; DARE, Database of Abstracts of Reviews of Effects; ITT, intention-to-treat; MD, mean difference; NA, not applicable; NR, not reported; OR, odds ratio; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review; USA, Unites States of America

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Poole 2016			
Citation			
Poole, D., Cortegiani, A., Chieregato, A., Russo, E., Pellegrini, C., De Blasio, E., . . . Tacconi, C. (2016). Blood component therapy and coagulopathy in trauma: A systematic review of the literature from the trauma update group. PLoS ONE, 11 (10) (e0164090). doi:http://dx.doi.org/10.1371/journal.pone.0164090			
Affiliation/Source of funds			
Funding: No funding was received for the review. The authors declared no conflicts of interest. *Author affiliations*: Trauma Update Working Group, Italy			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of controlled studies	I-III	Not reported	Trauma (military, obstetrical, and perioperative specifically excluded)
Prognostic factor		**Comparator**	
Hypofibrinogenemia, Platelet reduction, Increased APTT, Increased PT, Increased INR		NA	
Population characteristics			
Patients with non-TBI trauma.			
Length of follow-up		**Outcomes measured**	
Medline via PubMed searched between 9 December 2014 and 1 January 2000		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. Population inclusion was poorly defined, and list of excluded studies was not provided *Risk of bias of included studies:* The overall risk of bias for included studies was high, and quality of evidence according to the GRADE methodology was very low. There was high heterogeneity between studies and there was inadequate control for confounding.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**28-day Mortality** **n/N (%)**	**Risk estimate (95% CI)** **Odds ratio**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Fibrinogen			
Mortality N = 1650 (2 studies) Hagemo 2014 Low fibrinogen High fibrinogen Rourke 2012	 99/1133 (8.7) 62/517 (12.0)	 OR 0.08 (0.03–0.20) OR 1.77 (0.94–3.32) OR 0.22 (0.10–0.47)	NR

STUDY DETAILS: Poole 2016			
Platelet count			
Mortality N = 1464 (2 studies) Hagemo 2014 Mitra 2010	 99/1133 (8.7) 99/331 (29.9)	 OR 1 (1.0–1.0) OR 0.99 (0.99–0.99)	NR
INR			
Mortality N = 1464 (2 studies) Hagemo 2014 Mitra 2010	 99/1133 (8.7) 99/331 (29.9)	 OR 1.65 (0.65–4.18) OR 1.43 (1.02–2.01)	NR
PT			
Mortality N = 7638 (1 study) MacLeod 2003	 NR	 OR 1.35 (1.11–1.68)	NR
APTT			
Mortality N = 9336 (3 studies) Rourke 2012 MacLeod 2003 Sambavisan 2011	 62/517 (12.0) NR 173/1181 (14.6)	 OR 1.05 (1.01–1.09) OR 4.26 (3.23–5.62) OR 1.015 (1.01–1.02)	NR
EXTERNAL VALIDITY			
Generalisability (relevance of the study population to the Guidelines target population)			
The evidence is not directly generalisable to the Australian population but could be sensibly applied. Location of included studies is not reported; however, studies include a large number of patients and three studies (Hagemo 2014, Rourke 2012, and Sambavisan 2011) are multi-centre studies. Relevance to the target population is unclear.			
Applicability (relevance of the evidence to the Australian health care system)			
The evidence is probably applicable to the Australian healthcare context with some caveats. Location and setting is not specifically provided, however military, obstetrical, and perioperative publications have been specifically excluded, meaning the study may be applicable to general trauma setting in the Australian health care system.			
Additional comments			
Authors conclusions: Because of heterogeneity in design and definition of coagulopathy, evidence from different studies could not be combined. Each single study provided “very low” evidence according to GRADE methodology. There is significant uncertainty of the results. *Included studies:* Hagemo 2014, Mitra 2010, Rourke 2012, MacLeod 2003, Sambavisan 2011			

APTT, activated partial thromboplastin time; CI, confidence interval; INR, internal normalised ratio; ITT, intention-to-treat; MA, meta-analysis; MD, mean difference; NA, not applicable; NR, not reported; OR, odds ratio; PR, prothrombin time; PT, prothrombin time; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review; TBI, traumatic brain injury

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Levy 2017
Citation
Levy, J. H., Rossaint, R., Zacharowski, K., & Spahn, D. R. (2017). What is the evidence for platelet transfusion in perioperative settings? Vox Sanguinis, 112(8), 704-712. doi:http://dx.doi.org/10.1111/vox.12576
Affiliation/Source of funds
Funding: The study was funded by CSL Behring. *Author affiliations:* Steering committees for Boehringer Ingelheim, CSL Behring, Grifols and Instrumentation Labs.

STUDY DETAILS: Levy 2017			
Authors have received funding previously from Bayer Healthcare (Germany) and Boehringer Ingelheim (Germany), Abbott GmbH & Co KG, AbbVie Deutschland GmbH & Co KG, Aesculap Akademie GmbH, AQAI GmbH, Astellas Pharma GmbH, AstraZeneca GmbH, Aventis Pharma GmbH, B. Braun Melsungen AG, Baxter Deutschland GmbH, Biosyn GmbH, Biotest AG, Bristol-Myers Squibb GmbH, CSL Behring GmbH, Dr. F. Kohler Chemie GmbH, Dr€ager Medical GmbH, Essex Pharma GmbH, Fresenius Kabi GmbH, Fresenius Medical Care, Gambro Hospal GmbH, Gilead, GlaxoSmithKline GmbH, Gr€unenthal GmbH, Hamilton Medical AG, HCCM Consulting GmbH, Heinen+Lowenstein GmbH, Janssen-Cilag GmbH, Masimo, med Update GmbH, Medivance EU B.V., MSD Sharp & Dohme GmbH, Novartis Pharma GmbH, Novo Nordisk Pharma GmbH, P. J. Dahlhausen&Co. GmbH, Pfizer Pharma GmbH, Pulsion Medical Systems S.E., Siemens Healthcare, Teleflex Medical GmbH, Teva GmbH, TopMed Medizintechnik GmbH, Verathon Medical, Vifor Pharma GmbH and others.			
Study design	**Level of evidence**	**Location**	**Setting**
Narrative SR of prospective and retrospective studies	I-III	NR	Perioperative (cardiac surgery, acute aortic dissection, liver transplant)
Prognostic factor		**Comparator**	
Platelet count		NA	
Population characteristics			
Adult patients receiving platelet transfusion			
Length of follow-up		**Outcomes measured**	
Literature search was conducted in Medline (PubMed) on 28 March 2017		Platelet transfusion volume	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. Review did not provide sufficient details of included studies, did not provide list of excluded studies, did not conduct risk of bias, and did not conduct a meta-analysis. *Risk of bias of included studies:* Risk of bias not assessed or reported.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**Platelet transfusion** **n/N (%)** **Mean ± SD**	**No platelet transfusion** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Platelet count				
Platelet transfusion volume N = 30 735 (7 studies) Arnold 2006 Fayed 2013 McGrath 2008 Premaratne 2001 Tanaka 2014 Wu 2014 van Hout 2017	Heterogeneity between studies was so substantial that quantitative synthesis was not possible. Included studies used different measurements to trigger platelet transfusion, including platelet count, bleeding (visual measure), and viscoelastic measures. The platelet counts used as triggers varied between the two publications, ranging from a median of 51 (IQR 26–68) $\times 10^9$ /l for interventional treatment in a study evaluating patients in a mixed medical/surgical intensive care unit (Arnold 2006) to a trigger of <100 $\times 10^9$ /l accompanied by bleeding in cardiac surgery patients (van Hout 2017). Different platelet doses per transfusion were administered in all studies, ranging from 1 to 6-12 units (van Hout 2017, Tanaka 214, Fayed 2013). Wu 2014 and McGrath 2008 did not report a measurement for triggering transfusion or dose of transfusion administered. Premaratne 2001 observed a change in bleeding time (NR) between cardiopulmonary bypass patients who received < 10 units or > 10 units of platelet transfusions.			

EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. There is insufficient data provided on the included studies to determine if the findings are relevant to the guidelines target population.

STUDY DETAILS: Levy 2017
Applicability (relevance of the evidence to the Australian health care system)
The evidence is not applicable to the Australian healthcare context. There is insufficient data provided on the included studies to determine if the findings are applicable to the Australian health care system.
Additional comments
Authors conclusions: Platelet transfusion is an important facet of haemostatic management. However, the high degree of variation in the methods and outcomes of the published studies evaluated in this review make it difficult to draw conclusions as to recommendations for platelet transfusion, as no clear consensus was identified. there is a clear and urgent need for additional studies to assess the appropriate dose and triggers for platelet transfusion in perioperative patients and to investigate the suitability of current platelet transfusion guidelines in perioperative patients. *List of relevant included studies:* Arnold 2006, Fayed 2013, McGrath 2008, Premaratne 2001, Tanaka 214, Wu 2014, van Hout 2017

CI, confidence interval; ITT, intention-to-treat; IQR, inter quartile range; MD, mean difference; NA, not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Lilitis 2018			
Citation			
Lilitsis, E., Xenaki, S., Athanasakis, E., Papadakis, E., Syrogianni, P., Chalkiadakis, G., & Chrysos, E. (2018). Guiding management in severe trauma: Reviewing factors predicting outcome in vastly injured patients. Journal of Emergencies, Trauma and Shock, 11(2), 80-87. doi:http://dx.doi.org/10.4103/JETS.JETS-74-17			
Affiliation/Source of funds			
Funding: The study had no financial support or sponsorship. The authors declared no conflicts of interest. *Author affiliations:* University Hospital of Crete, Heraklion, Greece			
Study design	**Level of evidence**	**Location**	**Setting**
SR (narrative)	I-III	Not reported	Trauma
Prognostic factor		**Comparator**	
Vital signs (temperature), Lactate and base deficit, Coagulopathy		NA	
Population characteristics			
Severely injured trauma patients			
Length of follow-up		**Outcomes measured**	
PubMed, Cochrane database, and advanced trauma life support guiding manuals were searched for Citations published between 1994 and 2016.		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. Limited detail on search strategy, selection methods, data extraction, and study inclusion was provided. *Risk of bias of included studies:* There was no risk of bias assessment completed by the review authors.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**Intervention** **n/N (%)** **Mean ± SD**	**Comparator** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Temperature (hypothermia)				
Mortality N = 701 491, Martin 2005	25.5%	3.0%	NR	Significant association *p* = NR

STUDY DETAILS: Lilitis 2018				
N = NR, Balvers 2016	NR	NR	OR 2.82 (NR)	Significant association *p* = NR
Lactate levels and base deficit				
Mortality (3 studies) N = 1829, Gale 2016	A 1 mmol/L increase in lactate levels was associated with a 17% increase in mortality risk. A 1 mq/L increase in base deficit was associated with an approximate 4% increase in mortality risk.			Significant association *p* = NR
N = 4472, Odom 2013	<2.5 mmol/L OR: 1 (NR) 2.5–3.9 mmol/L OR: 1.5 (NR) >4 mmol/L OR: 3.8 (NR)			*p* = NR
N = 493, Heinonen 2014	<2.5 mmol/L was associated with a mortality rate of 22%[b] High lactate (not normalised within 24hrs) was associated with a mortality rate of 54%[b]			*p* = NR
Prothrombin				
Mortality N = NR (1 study) MacLeod 2003	Abnormal PT was associated with 35% greater risk			*p* = NR
APTT				
Mortality N = NR (1 study) MacLeod 2003	Elevated APTT was associated with 326% greater risk			*p* = NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. There is insufficient evidence presented in the review to determine generalisability of the evidence				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context. There is insufficient evidence presented in the review to determine applicability of the evidence.				
Additional comments				
Authors conclusions: The main mortality-predicting factors in trauma patients are lactate levels, temperature, and coagulopathy, and these should be identified and measured early by the treating physician. However, most studies were retrospective or observational, and as such are of low quality and high inherent bias *List of included studies:* Gale 2016, Odom 2013, Heinonen 2014, Mizusima 2011, Callaway 2009, Bohnen 2016, Victorino 2003, Strnad 2015, Sloan 2014, Rau 2016, Olaussen 2014, Pandit 2014, Kristensen 2016, Singh 2014, Luna 1987, Peng 1999, Perlman 2016, Martin 2005, Balvers 2016, Wang 2005, Andrews 2015, MacLeod 2003				

APTT, activated partial thromboplastin time; CI, confidence interval; ITT, intention-to-treat; MD, mean difference; NA, not applicable; NR, not reported; OR, odds ratio; PP, per-protocol; PT, prothrombin time; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. reported as survival rate and converted to mortality rate

c. defined as patients who did not achieve normal lactate within 48 hours of admission

STUDY DETAILS: Tran 2018
Citation
Tran, A., Matar, M., Lampron, J., Steyerberg, E., Taljaard, M., & Vaillancourt, C. (2018). Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: A systematic review and meta-analysis. *Journal of Trauma and Acute Care Surgery, 84*(3), 505-516. doi:http://dx.doi.org/10.1097/TA.0000000000001760

STUDY DETAILS: Tran 2018			
Tran, A., Matar, M., Steyerberg, E. W., Lampron, J., Taljaard, M., & Vaillancourt, C. (2017). Early identification of patients requiring massive transfusion, embolization, or hemostatic surgery for traumatic hemorrhage: a systematic review protocol. Systematic reviews, 6(1), 80. doi:10.1186/s13643-017-0480-0			
Affiliation/Source of funds			
The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of prospective and retrospective observational studies	I-III	USA, Europe, Asia, Australia	Trauma: Civilian 78 (92.9%) Military 6 (7.1%)
Prognostic Factor/s		**Comparator**	
Systolic Blood Pressure (SBP) Heart Rate (HR) Haemoglobin Lactate International normalised ratio (INR)		NA	
Population characteristics			
Adult patients with traumatic torso injuries. Studies of patients with isolated head injury without torso involvement, isolated traumatic limb amputation, isolated long bone fracture, or burn injury were excluded.			
Length of follow-up		**Outcomes measured**	
Medline and embase was searched between 1 January 1946 and 31 September 2016. Central Cochrane Library databases, and conference abstracts from Trauma Association of Canada, the American Association for the Surgery of Trauma, the Eastern Association for the Surgery of Trauma and the Trauma, Critical Care and Acute Care Surgery annual meetings were searched from 2014 to 2016. ClinicalTrials.gov registry was searched for in-progress studies.		Haemostatic surgical intervention, angiographic embolisation, or massive transfusion within 24 hours of hospital admission – which served as a surrogate for clinically significant bleeding.	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. The review does not include a list of excluded studies. The review does not disclose sources of funding. *Risk of bias of included studies:* The overall risk of bias for included studies was judged by the review authors to be high. Not all models were designed for the purpose of prediction, with confounding adjustment used in the evaluation of a single predictor. Study population was well defined in all studies. Justification for predictor selection and predictor measurement was poorly defined overall. Handling of data was frequently not reported. It is unclear how the bias is likely to impact the prognostic factor.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**SBP** **(log) odds ratio** **(SE)**	**Risk estimate** **Odds ratio (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Systolic Blood Pressure			
Significant bleeding N = NR (5 studies)		**3.95 (2.18, 7.15)**	*Favours hypotension* $p < 0.00001$
Callcut 2013	0.956 (0.142)	2.60 (1.97, 3.44)	Substantial heterogeneity
McLaughlin 2008	1.261 (0.33)	3.53 (1.85, 6.74)	$I^2 = 83\%$ ($p = 0.0001$)
Nunez 2009	2.565 (0.329)	13.00 (6.82, 24.77)	
Prichayudh 2014	1.552 (0.494)	4.72 (1.79, 12.43)	

STUDY DETAILS: Tran 2018			
Vandromme 2011	0.732 (0.253)	2.08 (1.27, 3.41)	
Heart Rate			
Significant bleeding N = NR (7 studies) Brasel 2007 Callcut 2013 Kaiser 2009 McLaughlin 2008 Nunez 2009 Prichayudh 2014 Vandromme 2011	 0.788 (0.193) 0.405 (0.117) 0.47 (0.236) 1.58 (0.32) 1.361 (0.302) 1.082 (0.326) 1.267 (0.239)	**2.57 (1.81, 3.67)** 2.20 (1.51, 3.21) 1.50 (1.19, 1.89) 1.60 (1.01, 2.54) 4.85 (2.59, 9.09) 3.90 (2.16, 7.05) 2.95 (1.56, 5.59) 3.55 (2.22, 5.67)	*Favours tachycardia* $p < 0.00001$ Substantial heterogeneity I2 = 77% ($p = 0.0002$)
Haemoglobin			
Significant bleeding N = NR (3 studies) Callcut 2013 Paulus 2014 Vandromme 2011	 0.875 (1.41) 0.94 (0.122) 2.315 (0.266)	**3.78 (1.97, 7.26)** 2.40 (1.82, 3.16) 2.56 (2.02, 3.25) 10.12 (6.01, 17.05)	*Favours low haemoglobin* $p < 0.0001$ Substantial heterogeneity $I^2 = 92\%$ ($p < 0.00001$)
Lactate			
Significant bleeding N = NR (2 studies) Vandromme 2010 Vandromme 2011	 1.649 (0.201) 1.141 (0.239)	**4.10 (2.50, 6.74)** 5.20 (3.51, 7.71) 3.13 (1.96, 5.00)	*Favours lactic acidosis* $p < 0.0001$ Substantial heterogeneity $I^2 = 62\%$ ($p < 0.10$)
INR			
Significant bleeding N = NR (2 studies) Callcut 2013 Vandromme 2011	 1.224(0.161) 1.725 (0.274)	**4.16 (2.57, 6.73)** 3.40 (2.48, 4.66) 5.61 (2.57, 6.73)	*Favours coagulopathy* $p < 0.00001$ Substantial heterogeneity $I^2 = 60\%$ ($p < 0.11$)
EXTERNAL VALIDITY			
Generalisability (relevance of the study population to the Guidelines target population)			
The evidence is directly generalisable to the Australian population with some caveats. The majority (92.9%) of studies were conducted in the civilian population. Excluding specified studies ensures critical bleeding is associated to volume lost, not location of the bleed. Inconsistencies in thresholds used between studies may lower the generalisability to the guideline's population.			
Applicability (relevance of the evidence to the Australian health care system)			
The evidence is probably applicable to the Australian healthcare context with some caveats. Six (7.1%) included studies were conducted in Australia or New Zealand. The majority (65.5%) of studies were conducted in the USA. All studies that reported participating centres were Level I trauma, major or university hospitals.			
Additional comments			
Authors conclusions: The author concluded there are no high quality, evidence-based prediction models for traumatic haemorrhage. Although the results for each outcome are highly significant, the results should be interpreted with caution due to the substantial heterogeneity between studies. *Included relevant studies:* Brasel 2007, Callcut 2013, Kaiser 2009, McLaughlin 2008 (Kauvar 2006), Nunez 2009, Paulus 2014, Prichayudh 2014, Vandromme 2010, Vandromme 2011			

CI, confidence interval; INR, international normalised ratio; ITT, intention-to-treat; MD, mean difference; not applicable, not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SE, standard error; SR, systematic review

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Kamyszek 2019			
Citation			
Kamyszek 2019 Kamyszek, R, W., Leraas, H, J., Reed, C., Ray, C. M., Nag, U, P., Poisson, J, L. & Tracy, E. T. 2019. Massive transfusion in the pediatric population: A systematic review and summary of best-evidence practice strategies. *Journal of Trauma Acute Care Surgery 86*(4): 744-754. doi: 10.1097/TA.0000000000002188			
Affiliation/Source of funds			
Authors declared they received no funding (p753) Author affiliations: The School of Medicine (R.W.K.) and Departments of Surgery (H.J.L., C.R., U.P.N., E.T.T.), Pediatrics (C.M.R.), and Pathology (J.L.P.), Duke University, Durham, North Carolina. The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of 29 Observational studies	I-III	NR	Paediatric trauma centre, hospital, military
Intervention		**Comparator**	
Massive blood transfusion		NA	
Population characteristics			
Pediatric population requiring massive blood transfusion (massive blood transfusion definition differed between included studies)			
Length of follow-up		**Outcomes measured**	
e.g. Citations published between January 1946 and December 2017		Mortality, Hours to first blood product, hours to first RBC, hours to first FFP, hours to first PLT	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious Description: More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. Included studies: e.g., the overall risk of bias for included studies was judged by the review authors to be high. There were concerns with patient selection bias due to significant differences in baseline characteristics of comparator groups and attrition bias due to incomplete reporting of outcome data, with no explanations given for missing data. The bias is likely to favour the intervention.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Post MTP (Massive transfusion protocol) implementation vs Before MTP implementation				
Mortality N = NR (3 studies) Hwu 2016 Chidester 2012 Hendrickson 2012	NR 47.1% 45% 38%	NR 53.8% 45% 23%	NR	$p = 0.729$ $p > 0.05$ $p = 0.10$
Hours to first blood product N = NR (1 study) Hwu 2016	Mean = 0.9	Mean = 0.8	NR	p= 0.688
Hours to first RBC	Mean = 1.4	Mean = 0.8	NR	p= 0.180

STUDY DETAILS: Kamyszek 2019				
N = NR (1 study) Hwu 2016				
Hours to first FFP N = NR (2 studies) Hwu 2016 Hendrickson 2012	 Mean = 1 Mean = 0.8	 Mean = 2.7 Mean = 3.3	NR	 p = 0.005 p < 0.001
Hours to first PLT N = NR (1 study) Hwu 2016	Mean = 4.4	Mean = 6.0	NR	p = 0.421
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context				
Additional comments				
Authors conclusions: This systematic review provides highlights of current practice strategies in pediatric MT. Our institutional experience is consistent with the broader national and international experience in regards tomortality and protocol adherence. Centers hold the potential to improve with respect to protocol adherence and systematic use of hemostatic adjuncts in this pediatric population. This review highlights the scattered, heterogeneous quality of studies in this field. Ultimately, prospective, multi-institutional studies would be helpful to more formally and systematically assess MTPs in this unique and diverse patient population to target optimal protocols and improve patient outcomes. *List of relevant included studies:* Shroyer 2017, Acker 2016, Horst 2016, Hwu 2016, Navarantnam 2016, Smith 2016, Sparkle 2016, Edwards 2015, Hwu 2015, Neff 2015, Eckert 2014, Kua 2014, Lee 2014, Livingston 2014, Agrawal 2013, Diab 2013, Huang 2013, Nosanov 2013, Arul 2012, Chidester 2012, Craig 2012, Hendrickson 2012, Dehmer 2010, Dressler 2010, Downes 2001, Buntain 1999, Brown 1990, Cote 1985, Schroeder 1969				

CI, confidence interval; ITT, intention-to-treat; MD, mean difference; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Shih 2019			
Citation			
Shih, AW., Al Khan, S., Wang, AY., Dawe, P., Young, PY., Greene, A., Hudoba, M. & Vu, E. 2019. Systematic reviews of scores and predictors to trigger activation of massive transfusion protocols. *Journal of Trauma and Acute Care Surgery, 87*(3). 717-729. doi: 10.1097/TA.0000000000002372			
Affiliation/Source of funds			
Details on funding not provided. *Author affiliations:* the Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada (A.W.S., A.Y.W., M.H.)., Vancouver Coastal Health Authority Vancouver, British Columbia, Canada (A.W.S., P.H., P.Y.Y., M.H., E.V.)., Blood Banks Services, Directorate General of Specialized Medical Care Ministry of Health, Oman (S.A.)., Department of Surgery, University of British Columbia, Vancouver, British Columbia, Canada (P.W.)., Critical Care Transport Program, British Columbia Emergency Health Services, Vancouver, British Columbia, Canada (A.G., E.V.)., Department of Emergency Medicine, University of British Columbia, Vancouver, British Columbia, Canada (E.V.). & Department of Critical Care Medicine University of British Columbia, Vancouver, British Columbia, Canada (E.V.). *Conflict of interest*: A.W.S. is a consultant for Octapharma Canada. The other authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of observational studies	I-III	Not reported	Trauma

STUDY DETAILS: Shih 2019				
Prognostic Factors			**Comparator**	
Temperature, INR, Haemoglobin, ionized calcium, Fibrinogen			NA	
Population characteristics				
Not reported				
Length of follow-up			**Outcomes measured**	
Not reported			Transfusion volume	
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The Newcastle-Ottawa Scale was used to assess the bias of included studies. It was deemed that the majority of case-control studies defined cases and had appropriate representativeness of cases, but some did not always provide detail on different characteristics of controls or what the definition of controls were. Some case-control studies also did not provide details for patients that were lost to follow-up. Cohort studies included were of good methodological quality based on assessment using the Newcastle-Ottawa Scale.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Temperature (<35.5°C) versus Temperature (>35.5°C)				
RBC transfusion volume (≥ 10 units in 6 hrs) N = 170 (1 CC) Callcut 2011	NR	NR	OR 4.0 (1.6, 10.1)	NR
INR (>1.5) versus INR (<1.5)				
RBC transfusion volume (≥ 10 units in 6 hrs) N = 170 (1 Study) Callcut 2011	NR	NR	OR 11.3 (2.7, 47.3)	NR
RBC transfusion volume (≥ 10 units in 24 hrs) N = 1803 (2 Studies) Callcut 2013 (N = 1245) Schreiber 2007 (N = 558)	NR	NR	NR OR 2.1 (1.4, 3.1) OR 5.9 (3.5, 10.2)	NR
Haemoglobin (< 11 g/dL) versus Haemoglobin (> 11 g/dL)				
RBC transfusion volume (≥ 10 units in 6 hrs) N = 2349 (5 studies) Callcut 2011 (N = 170) Callcut 2013 (N = 1245) Leemann 2010 (N = 53) Schöchl 2011 (N = 323) Schreiber 2007 (N = 558)	NR	NR	NR OR 3.1 (1.2, 8.4) OR 1.8 (1.3, 2.5) OR 18.18 (2.73, 125.00) ROC AUC 0.87 (0.83, 0.91) OR 7.7 (5.0, 11.9)	NR
Ionized Calcium (<1 mmol/L) versus Ionized Calcium (>1 mmol/L)				
RBC transfusion volume (≥ 5 units in 24 hrs) N = 591 (1 Study)	NR	NR	NR	NR

STUDY DETAILS: Shih 2019				
Magnotti 2011			OR 2.294 (1.053, 4.996)	
Fibrinogen (≤190 mg/dL) versus Fibrinogen (>190 mg/dL)				
RBC transfusion volume (≥ 10 units in 24 hrs) N = 625 (1 Study) Nakamura 2017	NR	NR	NR OR 0.931 (0.898, 0.963)	NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. It is difficult to determine the applicability, the authors did not mention the location where the studies were performed.				
Additional comments				
Authors conclusions: The use of scores or tools to predict MTP need to be individualized to hospital resources and skill set to aid clinical judgment. Future studies for triggering non-trauma MTP activations are needed. *Included studies* Brooke 2016, Callcut 2011, Callcut 2013, Charbit 2013, David 2017, Kyoung 2016, Leemann 2010, Magnotti 2011, Nakamura 2017, Schochl 2011, Schreiber 2007				

CI, confidence interval; INR, International Normalised Ratio; MTP, massive transfusion protocol; NA, not applicable; NR, not reported; OR, odds ratio; pRBC, packed red blood cells; ROC AUC, received operating characteristic area under the curve; SD, standard deviation; SR, systematic review

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Vasudeva 2021			
Citation			
Vasudeva M, Mathew JK, Groombridge C, Tee JW, Johnny CS, et al. Hypocalcemia in trauma patients: a systematic review. *Journal of Trauma and Acute Care Surgery*. 2021; 90(2): 396-402			
Affiliation/Source of funds			
The authors declared no conflicts of interest. The source of funding was not reported. *Author affiliations:* National Trauma Research Institute, Alfred Health, Melbourne, Australia; Emergency and Trauma Centre and Trauma Service, The Alfred Hospital, Melbourne Australia; Central Clinical School, Monash University, Victoria, Australia; Software & Innovation Lab, Deakin University, Victoria Australia; Department of Neurosurgery, The Alfred Hospital, Melbourne, Australia.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of observational studies	I-III	Cherry 2006: US Magnotti 2011: US Vasudeva 2020: Australia	Trauma centres
Intervention		**Comparator**	
Ionized hypocalcaemia (<1.11 mmol/L)		NA	
Population characteristics			
Trauma patients (≥18 years) with an admission ionized calcium measurement before blood transfusion			
Length of follow-up		**Outcomes measured**	
Authors searched MEDLINE from data inception to 3 May 2020 PROSPERO CRD42020105135		Mortality Transfusion requirements	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low			

STUDY DETAILS: Vasudeva 2021				
Description: More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The overall risk of bias was moderate. The authors noted that Vasudeva 2020 was limited by small sample size, and the systematic review was subject to publication bias.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**Hypocalcaemia** **n/N (%)** **Mean ± SD**	**Normocalcemia** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Mortality N = 1213 (3 studies)				
Cherry 2006	24/91 (26.4)	48/305 (15.7)	OR 1.92 (NR)	*p* <0.05
Magnotti 2011	NR/332 (15.5)	NR/259 (8.7)	NR	*p* = 0.036
Vasudeva 2020	29/113 (25.6)	17/113 (15.0)	NR	*p* = 0.047
Transfusion N = 817 (2 studies)				
Magnotti 2011				
≥5 U	NR/332 (17.1)	NR/259 (7.1)	NR	*p* = 0.005
≥10 U	NR/332 (8.2)	NR/259 (2.2)	NR	*p* = 0.017
Vasudeva 2020	75/113 (62.5)	45/113 (37.5)	NR	*p* <0.001
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context. Vasudeva 2020 was conducted in Australia.				
Additional comments				
Authors conclusions: moderate quality evidence on the association between transfusion-independent hypocalcaemia and mortality, blood transfusion needs, and coagulopathy. However, further prospective trials are needed to corroborate this relationship and identify possible therapeutic measures that might mitigate the aforementioned outcomes. *Included studies:* Cherry 2006, Magnotti 2011, Vasudeva 2020				

CI, confidence interval; MD, mean difference; NA, not applicable; NR, not reported; OR, odds ratio; SD, standard deviation; SR, systematic review; U, unit; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

Prospective cohort studies

STUDY DETAILS: Magnotti 2011			
Citation			
Magnotti LJ, Bradburn EH, Webb DL, Berry SD, Fischer PE, Zarzaur BL, et al. Admission ionized calcium levels predict the need for multiple transfusions: A prospective study of 591 critically ill trauma patient. Journal of Trauma - Injury, Infection and Critical Care. 2011;70(2):391-7. doi: 0.1097/TA.0b013e31820b5d98			
Affiliation/Source of funds			
None reported			
Study design	**Level of evidence**	**Location**	**Setting**
Prospective cohort study	III	Tennessee, USA	Regional trauma centre
Prognostic factor		Comparator	
Ionized Calcium (iCa) levels		NA	
Population characteristics			
Civilians admitted to the trauma centre after a trauma activation and have not received any blood product transfusion before arrival at the trauma centre			
Length of follow-up		**Outcomes measured**	
Study conducted over 9 months. Follow-up for all outcomes was 24h		Mortality, Multiple transfusions (>4 units packed RBCs in 24 hrs), Massive transfusion (<9 units packed red blood cells in 24 hrs)	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has plausible bias that seriously weakens confidence in the results. Blinding of prognostic factor or outcomes (mortality, multiple transfusions or massive transfusions) in the study were not reported and the study did not report on dropouts or loss to follow up.			
RESULTS			
Outcome	**Prognostic factor (%)**	***p*-value**	
Mortality N = 591	Hi-Cal (iCa ≥ 1.00): NR/259 (8.7) Lo-Cal (iCa < 1.00): NR/332 (15.5)	0.036	
Multiple transfusions N = 591	Hi-Cal: NR/259 (7.1) Lo-Cal: NR/332 (17.1)	0.005	
Massive transfusion N = 591	Hi-Cal: NR/259 (2.2) Lo-Cal: NR/332 (8.2)	0.017	
Outcome	**Variable**	**Odds ratio**	**95% CI**
Multiple transfusions	iCa < 1.00	2.29	1.05- 5.00
EXTERNAL VALIDITY			
Generalisability (relevance of the study population to the Guidelines target population)			
The evidence is not directly generalisable to the Australian population, and it is hard to judge whether it is sensible to apply. There is very little information (age only) given on the characteristics of the included population.			
Applicability (relevance of the evidence to the Australian health care system)			
The evidence is not applicable to the Australian healthcare context. A single trauma care centre in USA likely has significant differences compared to the Australian health care system.			
Additional comments			
Authors conclusions: It should be noted that admission iCa was similar to both admissions BE and lactate in this regard. Thus, iCa may serve as an adjunct to these values in the initial phase of resuscitation			

CI, confidence interval; dL; decilitre; h, hour; Hb, haemoglobin; HR, heart rate; iCa, ionized calcium; mEq, milliequivalent; mmol; millimoles; NA, not applicable; NPV, negative predictive value; NR, not reported; PPV; positive predictive value; SBP, systolic blood pressure; SI, shock index

STUDY DETAILS: Javali 2017			
Citation			
Javali, R. H., Ravindra, P., Patil, A., Srinivasarangan, M., Mundada, H., Adarsh, S. B., & Nisarg, S. (2017). A Clinical Study on the Initial Assessment of Arterial Lactate and Base Deficit as Predictors of Outcome in Trauma Patients. Indian J Crit Care Med, 21(11), 719-725. doi:10.4103/ijccm.IJCCM_218_17			
Affiliation/Source of funds			
The study received no financial support or sponsorship. The authors declared no conflicts of interest. *Author affiliations*: PR affiliated with Department of Emergency Medicine, Kasturba Medical College, Manipal, Karnataka, India; HM affiliated with Department of Emergency Medicine, St. John's Medical College and Hospital, Bengaluru, Karnataka, India			
Study design	**Level of evidence**	**Location**	**Setting**
Prospective cohort study	II	India	Tertiary care centre ED
Prognostic factor		**Comparator**	
Lactate, Base deficit, blood pressure, heart rate, haemoglobin, shock index		NA	
Population characteristics			
100 trauma patients (penetrating trauma to chest, abdomen, or pelvis, pelvis fracture, shaft of femur fracture, blunt injury to abdomen or chest) at risk of haemodynamic compromise.			
Length of follow-up		**Outcomes measured**	
Study conducted over 18 months. Follow-up for all outcomes was 24h		Mortality at 24h Blood transfusion received at 24h	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has plausible bias that seriously weakens confidence in the results. Enrolled patients were not from a consecutive cohort, there was inadequate control of confounding factors. Study enrolled 100 patients however only 92 were included in analysis of base deficit (see Table 1 of study) and study does not give reason why.			
RESULTS			
Outcome No. patients (No. trials)	**[intervention] n/N (%)**	**[comparator] n/N (%)**	**Risk estimate (95% CI) OR**	***Statistical significance* *p*-value Heterogeneity[a] I^2 (*p*-value)**
Arterial lactate				
Mortality, 24 hours	Difference between 24 h mortality for arterial lactate <4 mmol/L (0%) and ≥ 4 mmol/L (38.1%) was statistically significant ($p < 0.001$)			
Blood requirement, 24 hours	Difference in blood requirement among the patients with lactate <2.9 mmol/L (24.6%) and lactate ≥2.9 mmol/L (85.7%) was statistically significant ($p < 0.001$)			
Base-deficit				
Mortality, 24 hours	Base-deficit of ≥12 mEq/L showed a 30.4% increased risk of mortality compared to below <12 mEq/L (1.3%).			
Blood requirement, 24 hours	Base-deficit of ≥12 mEq/L showed a 78.3% increased risk of blood transfusion requirement compared to below <12 mEq/L (36.4%).			
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. There is very little information (age only) given on the characteristics of the included population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context. A single tertiary care centre in India likely has significant differences compared to the Australian health care system.				

STUDY DETAILS: Javali 2017
Additional comments
Authors conclusions: Emergency admission arterial lactate and Base Deficit are useful in predicting 24 h mortality, blood transfusion requirement and ICU admission. These values can be used to triage, identify shock early, assess transfusion requirement, and prognosticate trauma patients.

CI, confidence interval; dL; decilitre; ED, emergency department; h, hour; Hb, haemoglobin; HR, heart rate; ICU, intensive care unit; mEq; milliequivalent; mmol; millimoles NA, not applicable; NPV, negative predictive value; NR, not reported; PPV; positive predictive value; SBP, systolic blood pressure; SI, shock index

STUDY DETAILS: Gaessler 2021			
Citation			
Gaessler H, Helm M, Kulla M, Hossfeld B, Schmid U, Kerchowski J, Bretschneider I. 2021. Prehospital evaluation and detection of induced coagulopathy in trauma: The PREDICT study. *Journal of Trauma and Acute Care Surgery, 91*(2). 344-351. doi: 10.1097/TA.0000000000003246			
Affiliation/Source of funds			
Funding: None declared. *Author affiliations:* Armed Forces Medical Centre Ulm, Department of Anaesthesiology and Intensive Care Medicine, Ulm, Germany. *Conflicts of interest*: Kulla M received research grants from the German Interdisciplinary Association of Critical Care and Emergency Medicine, German Federal Ministry of Education and Research and personal fees from Boehringer Ingelheim. All other authors declared no conflict of interest			
Study design	**Level of evidence**	**Location**	**Setting**
Prospective observational study.	III-2	Ulm, Germany	Two level I trauma centres
Intervention		**Comparator**	
Prognostic parameters assessed by ROTEM		NA	
Population characteristics			
148 trauma patients ≥ 18 years of age, non-pregnant, no pre-existing coagulation disorders, not receiving TXA before arrival to centre and ROTEM assay performed ≤ 120 minutes.			
Length of follow-up		**Outcomes measured**	
Follow-up at day 28 or hospital discharge. Six patients who were not transported to one of the two participating hospitals were excluded.		28-day mortality Transfusion requirement Detection of early coagulopathy after trauma TIC-associated changes in blood gas analyses *The aim of the study was to determine whether prognostic parameters (pH, lactate, base excess, haemoglobin) have an impact on the likelihood of developing TIC and HF	
Method of analysis			
The anonymised data sets were summarised using Microsoft Excel 2016. All parameters of the three defined groups were analysed with one-way analysis of variance. For the subgroup analysis with TICCS of ≥ 10, normal distribution of all parameters was tested using the Shapiro-Wilk test. Normally distributed parameters were analysed with the independent sample *t* test and nonnormally distributed parameters with the Mann-Whitney *U* test.			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has some important problems and cannot be considered comparable to a well-performed randomised trial.			

STUDY DETAILS: Gaessler 2021				
RESULTS				
Population analysed	**Intervention**		**Comparator**	
Available	148		NA	
Analysed	148		NA	
Outcome	**Intervention** **n/N (%)** **Mean ± SD**	**Comparator** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value**
Prognostic parameters				
Mortality	The study found that TIC and TIC with HF resulted in worse prognosis for mortality compared to those without coagulopathy. However, no data reported on prognostic factors and their association with outcomes of mortality or transfusion requirements. A correlation between prognostic indicators and mortality could not be determined.			
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The study included all trauma patients regardless of the severity of injury. However, the study was performed only in patients who required helicopter emergency medical services.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context. The study was performed in Germany which is similar to the Australian healthcare system.				
Additional comments				
Authors conclusions: In severely injured patients, TIC and HF can already be present at the site of incidence and do not only develop during medical treatment and transport. Significant changes in blood gas analysis parameters are associated with the presence of HF at the incidence site. In patients with TICCS of ≥10 points, TIC and HF are significantly more frequent. Future studies should investigate the predictive value of prehospital blood gas parameters and TICCS in terms of TIC and HF.				

CI, confidence interval; HF, hyperfibrinolysis; not applicable, not applicable; ROTEM, rotational thromboelastometry; SD, standard deviation; TIC, trauma-induced coagulopathy; TICCS, trauma-induced coagulopathy clinical score; TXA, tranexamic acid.

Retrospective cohort studies

STUDY DETAILS: Sawamura 2009					
Citation					
Sawamura A, Hayakawa M, Gando S, Kubota N, Sugano M, Wada T, Katabami, K. 2009. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. *Thrombosis Research.124*(5):608-13. doi:10.1016/j.thromres.2009.06.034					
Affiliation/Source of funds					
No conflicts of interests were declared. Authors declared no sources of funding. Author Affiliations: Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Japan. (All authors).					
Study design	**Level of evidence**		**Location**		**Setting**
Retrospective cohort study	III-3		NR		Emergency Department (ED)
Prognostic factor			**Comparator**		
Fibrinogen Prothrombin time platelets			NA		
Population characteristics					
all consecutive severe trauma patients defined as Injury Severity Score (ISS) ≥9					
Length of follow-up			**Outcomes measured**		
7-year study period (June 2000 to July 2007)			Mortality Massive Bleeding		
INTERNAL VALIDITY					
Overall risk of bias (descriptive)					
Rating: Moderate *Description:* The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.					
RESULTS					
Prognostic factor	**Outcome**	**AUC**	**Optimal Cutoff**	**Sensitivity (%)**	**Specificity (%)**
Fibrinogen	Mortality	0.828	1.9g/L	74.1	71.3
	Massive bleeding	0.810	1.9g/L	77.8	3.2
	Survivors (N = 259)		**Mortality (N = 55)**	**OR**	***p* value**
Prothrombin time (sec)	13.4 ± 1.8 (NR)		19.7±16.4 (NR)	NR	$p = 0.000$
Fibrinogen (g/L)	2.53 ± 0.9 (NR)		1.44 ± 0.8 (NR)	0.989 (0.979, 0.998)	$p = 0.015$
Platelet count (10^9/L)	159 ± 79 (NR)		147 ± 82 (NR)	1.097 (1.003, 1.116)	$p = 0.003$
Lactate (mmol/L)	NR		NR	1.236 (1.016, 1.502)	$p = 0.034$
EXTERNAL VALIDITY					
Generalisability (relevance of the study population to the Guidelines target population)					
The evidence is not directly generalisable to the Australian population and cannot be sensibly applied to the Australian setting					
Applicability (relevance of the evidence to the Australian health care system)					
The evidence may not be applicable to the Australian healthcare context as the study did not report the location(s) of study data					

STUDY DETAILS: Sawamura 2009
Additional comments
Authors notes:
Low fibrinogen level and a high FDP level within 4 hr after the onset of trauma are all considered to be independent predictors of death for trauma patients

CI, confidence interval; dL; decilitre; h, hour; Hb, haemoglobin; HR, heart rate; mEq; milliequivalent; mmol; millimoles; NA, not applicable; NPV, negative predictive value; NR, not reported; PPV; positive predictive value; SBP, systolic blood pressure; SI, shock index

STUDY DETAILS: Kawatani 2016			
Citation			
Kawatani Y, Nakamura Y, Kurobe H, Suda Y, Hori T. 2016 Correlations of perioperative coagulopathy, fluid infusion and blood transfusions with survival prognosis in endovascular aortic repair for ruptured abdominal aortic aneurysm. *World journal of emergency surgery: WJES*.11(29). 1-6. doi: 10.1186/s13017-016-0087-0			
Affiliation/Source of funds			
No conflicts of interests were declared. Authors declared no external funding *Author affiliation*: Department of Cardiovascular Surgery, Chiba-Nishi General Hospital, 107-1 Kanegasaku, Matsudo-Shi 2702251, Chiba-Ken, Japan (TH).			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort study	III	Japan	Surgical, Chiba-Nishi General Hospital
Prognostic factor		**Comparator**	
INR APTT Platelet count		NA	
Population characteristics			
Perioperative patients			
Length of follow-up		**Outcomes measured**	
Study period was from October 2013 to December 2015 with 24 hours and 30 day follow up		Mortality	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has some important problems relating to patient selection bias. Decisions to perform EVAR over standard open repair may influence the results.			

RESULTS

Outcome	**Prognostic factor**	**Survival**	**Non-survival**	***p*-value**
24-hour survival	**n**	**22**	**3**	NR
	Preoperative APTT (seconds)	27.0 +/- 4.3	33.6 +/- 8.4	0.21
	Postoperative APTT (seconds)	38.9 +/-8.7	108.7 +/- 63.4	0.006
	APTT change (seconds)	11.9 +/- 9.2	75.0 +/- 58.9	0.006
	Preoperative PT-INR	1.2 +/- 0.16	1.2 +/- 0.2	0.802
	Postoperative PT-INR	1.3 +/- 0.2	1.5 +/- 0.28	0.295
	Preoperative Platelet count (10^4/uL)	16.1 +/- 5.4	17.3 +/- 3.0	0.616
	Postoperative Platelet count (10^4/uL)	10.2 +/- 5.0	7.7 +/- 1.9	0.558
	Platelet count change (10^4/uL)	5.9 +/- 6.2	9.5 +/- 5.2	0.452
30-day survival	**n**	**20**	**5**	NR
	Preoperative APTT (seconds)	26.8 +/- 4.3	32 +/- 7.0	0.119
	Postoperative APTT (seconds)	38.1 +/- 7.9	95.7 +/- 57.9	0.002
	APTT change (seconds)	11.3 +/- 8.9	62.7 +/- 54.1	0.002
	Preoperative PT-INR	1.2 +/- 0.16	1.23 +/- 0.19	0.0767

STUDY DETAILS: Kawatani 2016				
	Postoperative PT-INR	1.4 +/- 0.2	1.5 +/- 0.2	0.148
	Preoperative Platelet count (10^4/uL)	16.2 +/- 5.54	16.8 +/- 2.7	0.767
	Postoperative Platelet count (10^4/uL)	10.4 +/- 5.0	7.2 +/- 1.9	0.299
	Platelet count change (10^4/uL)	-57 +/- 6.3	-9.6 +/- 4.0	0.335
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population as findings are on a small specific population with a specific condition and cannot be sensibly applied to the Australian setting				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence may not be applicable to the Australian healthcare context as the study did not report the location(s) of study data				
Additional comments				
Authors notes: Study focussed on perioperative patients with endovascular aortic repair. This was a very small population (n = 25). At both 24-h and 30 days post operation, there were no significant differences in preoperative APTT, PT-INR, or major coagulopathy between the survival groups and non-survival groups				

APTT, activated partial thromboplastin time; CI, confidence interval; dL; decilitre; h, hour; Hb, haemoglobin; HR, heart rate; INR, international normalised ratio; mEq; milliequivalent; mmol; millimoles NA, not applicable; NPV, negative predictive value; NR, not reported; PPV; positive predictive value; PT, prothrombin time; SBP, systolic blood pressure; SI, shock index

STUDY DETAILS: Noorbhai 2016			
Citation			
Noorbhai, MA., Cassimjee, HM., Sartorius, B. & Muckart, DJJ. 2016. Elevated international normalised ratios correlate with severity of injury and outcome. *South African Medical Journal 106*(11), 1141-1145. doi: 10.7196/SAMJ.2016.v106i11.10356			
Affiliation/Source of funds			
The authors declared no information on potential conflicts of interest. The authors provided no details on external funding *Author affiliations:* Department of General Surgery, School of Clinical Medicine, College of Health Sciences, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa (MAN); Trauma Unit and Trauma Intensive Care, Inkosi Albert Luthuli Central Hospital, Durban, South Africa (HMC); Discipline of Public Health Medicine, School of Nursing and Public Health, College of Health Sciences, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa (BS) Trauma Unit and Trauma Intensive Care, Inkosi Albert Luthuli Central Hospital, Durban, South Africa (DJJM)			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort	III	Durban, South Africa	Level 1 Trauma centre
Intervention		**Comparator**	
INRs ≤ 1.20		INRs > 1.20	
Population characteristics			
Of the 1000 patients included, 752 were male with an average age of 29 (median of 27). 36.9% of patients were aged between 21-30 years old. 16.5% were <16 years old. 1.6% were >70 years old.			
Length of follow-up		**Outcomes measured**	
First 1000 patients during 2007-2011		Mortality	
Method of analysis			
Multiple Poisson regression analysis			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has important problems relating to insufficient adjustment for confounders			

STUDY DETAILS: Noorbhai 2016				
RESULTS				
Population analysed	**Intervention (INRs ≤ 1.20)**		**Comparator (INRs > 1.20)**	
Available	454 (48.3%)		485 (51.7%)	
Analysed	454		485	
Outcome	**Intervention n/N (%) Mean ± SD**	**Comparator n/N (%) Mean ± SD**	**Adjusted Risk Ratio (95% CI)**	***Statistical significance p*-value**
External admissions (Scene) INRs ≤ 1.20 v INRs > 1.20				
Mortality N = 228	15/121 (12.4%)	44/107 (41.1%)	aRR 3.68 (2.11, 6.44)	$p < 0.001$
Inter-hospital transfers (non-scene) INRs ≤ 1.20 v INRs > 1.20				
Mortality N = 711	59/361 (16.3%)	88/350 (25.1%)	aRR 1.54 (1.15, 2.05)	$p = 0.004$
All INRs ≤ 1.20 v INRs > 1.20				
Mortality N = 939	74/482 (15.4%)	132/457 (28.9%)	aRR 1.92 (1.49, 2.48)	$p < 0.001$
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The study was performed in patients with trauma with no restriction on severity or mechanism of trauma.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The study was performed in South Africa which has a different healthcare system to Australia.				
Additional comments				
Authors conclusions: INRs were associated with worse outcomes. There was a direct correlation between INRs and ISSs. The INR may help identify patients at risk in resource-depleted environments. Further studies will assist in identifying optimal overall cut-off values for INR, ISS and ISS subgroups that would help identify patients at risk. Earlier recognition of ACoTS may help reduce mortality				
aRR, adjusted risk ratio; CI, confidence interval; INR, international normalised ratio; ISS, injury severity score; SD, standard deviation				

STUDY DETAILS: McQuilten 2017a
Citation
McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: A five-year statewide cohort study. Injury. 2017;48(5):1074-1081. doi:10.1016/j.injury.2016.11.021
Affiliation/Source of funds
Author affiliations: Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne, Australia; Transfusion Research Unit, Monash University, Melbourne, Australia. Electronic address: zoe.mcquilten@monash.edu. 2Transfusion Research Unit, Monash University, Melbourne, Australia. 3Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne, Australia. 4Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia. Conflict of interest: The authors have no conflict of interest to disclose. Funding: ZM is supported through an Australian National Health and Medical Research Council (NHMRC) Centre of Research Excellence for Patient Blood Management in Critical Illness and Trauma (APP1040971). The Victorian State Trauma Registry (VSTR) is a Department of Health and Human Services, State Government of Victoria and Transport Accident Commission funded project.

STUDY DETAILS: McQuilten 2017a			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort	III-3	2 Level I trauma centres, Australia	Victorian State Trauma Registry
Prognostic factor		**Comparator**	
Fibrinogen concentration		N/A	
Population characteristics			
Patients aged 18 or older who presented to the two major trauma hospitals and who had a fibrinogen level measured during initial resuscitation. major trauma were defined as those meeting any of the following criteria: - Death after injury; - An Injury Severity Score (ISS) >15 - Admission to an intensive care unit (ICU) requiring mechanical ventilation for at least part of their ICU stay - Urgent surgery for intrathoracic, intracranial, intra-abdominal procedures, or fixation of pelvic or spinal fractures.			
Length of follow-up		**Outcomes measured**	
between January 2008 and July 2011.		Mortality Transfusion volume (RBC, FFP, PLT, Cryoprecipitate or FC)	
Method of analysis			
The association between first fibrinogen levels and in-hospital mortality was modelled using multiple logistic regression. Variables considered included age, gender, ISS, pH, temperature, GCS, injury type (blunt, penetrating, other), chest decompression, pulse and systolic BP on admission, time from injury to admission, Hb, platelet count, INR, aPTT and fibrinogen level. As there were a high proportion of patients with missing values, we included a missing category for those variables with high missing rates (>5% of patients). The relationship was modelled in two ways, with fibrinogen treated as a continuous variable, and categorised as outlined above. The models were constructed using both stepwise selection and backwards elimination techniques before undergoing a final assessment for clinical and biological plausibility. Predicted mortality across the range of fibrinogen values was estimated using multiple logistic regression. The association between hospital and ICU LOS in survivors was modelled using linear regression with ICU LOS log-transformed. Sensitivity analysis for the association between mortality and fibrinogen levels was performed. As there were a high proportion of patients with missing values, we repeated our regression analysis using only patients with complete data to assess if the inclusion of missing category altered the findings of the regression analysis. Predictors for low fibrinogen (defined as <1.5g/L) on initial presentation were modelled using multiple logistic regression, including categories for missing values as in the mortality model. Descriptive statistics are reported as mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Hypothesis testing was performed using Chi Square for categorical data and either t-test or Wilcoxon rank sum for continuous data depending on data distribution. Fibrinogen was categorised as 4g/L to incorporate the normal reference range, as well as the commonly used thresholds for fibrinogen supplementation. The GCS was categorised according to clinical convention with 3 to 8 representing severe, 9 to 12 moderate and 13 to 15 a mild head injury. Temperature and pH were categorised according to normal ranges, with categories for below, within and above the normal range. Platelet count was categorised according to normal range, with categories for below normal range, and INR was categorised according to normal range, with categories for above normal range. Patient age and ISS were categorised into quintiles. Patients were categorized as having received a massive transfusion if they had received 10 or more units of red blood cells (RBC) during the admission. To increase the robustness of the study, a two-sided p-value of <0.01 was used to indicate statistical significance			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Moderate *Description:* The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.			

STUDY DETAILS: McQuilten 2017a				
RESULTS				
Outcome	**[intervention] n/N (%) median (IQR)**	**[reference] n/N (%) median (IQR)**	**Risk estimate (95% CI)**	***Statistical significance p*-value Heterogeneity[a] I^2 (*p*-value)**
Temperature				
Mortality, in-hospital N = 4773 <35 °C 35 to 36.5 °C >37.5 °C missing <35 °C 35 to 36.5 °C >37.5 °C	 n=428 n=1732 n=295 n=536	36.6 to 37.5°C (reference) n=1782	Unadjusted OR OR 9.56 (7.09, 12.89) OR 2.12 (1.62, 2.79) OR 0.85 (0.46, 1.57) Adjusted OR: OR 1.91 (1.28, 2.85) OR 1.11 (0.80, 1.56) OR 0.597 0.72 (0.35, 1.50)	Unadjusted: *p* < 0.001 *p* < 0.001 *p* = 0.57 Adjusted: *p* = 0.002 *p* = 0.53 *p* = 0.38
INR				
Mortality, in-hospital N = 4773 1.5 to 1.9 >2..0 1.5 to 1.9 >2..0		<1.5 (reference)	Unadjusted OR OR 10.26 (7.48, 14.05) OR 13.29 (9.43, 18.74) Adjusted OR: OR 3.23 (2.12, 4.92) OR 3.02 (1.82, 5.03)	Unadjusted: *p* < 0.001 *p* < 0.001 Adjusted: *p* < 0.001 *p* < 0.001
Platelet count				
Mortality, in-hospital N = 4773 <100 100 to 150 <100 100 to 150		>150 x10^9 /L (reference)	Unadjusted OR OR 4.44 (3.20, 6.16) OR 2.56 (1.97, 3.32) Adjusted OR: OR 0.50 (0.30, 0.84) OR 0.98 (0.69, 1.40)	Unadjusted: *p* < 0.001 *p* < 0.001 Adjusted: *p* = 0.009 *p* = 0.91
Fibrinogen concentration				
Mortality, in-hospital N = 4773 <1 g/L 1.0-1.5 g/L 1.6-1.9 g/L >4 g/L <1 g/L 1.0-1.5 g/L 1.6-1.9 g/L >4 g/L	 54/114 (47.4) 71/283 (25.1) 77/617 (12.5) 53/735 (7.2) 54/114 (47.4) 71/283 (25.1) 77/617 (12.5) 53/735 (7.2)	2 g/L (reference) 186/3024 (6.2)	Unadjusted OR OR 13.73 (9.24, 20.41) OR 5.11 (3.75, 6.94) OR 2.18 (1.64, 2.89) OR: 1.19 (0.86, 1.63) Adjusted OR* OR 3.28 (1.71, 6.28) OR 2.08 (1.36, 3.16) OR 1.39 (0.97, 2.00) OR 1.04 (0.70, 1.52)	Unadjusted: *p* < 0.001 *p* < 0.001 *p* < 0.001 *p* = 0.291 Adjusted: *p* < 0.001 *p* = 0.001 *p* = 0.08 *p* = 0.86
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. The study was conducted in Australia				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context. The study was conducted in Australia				

STUDY DETAILS: McQuilten 2017a
Additional comments
Authors conclusions: low initial fibrinogen concentrations was associated with increased in-hospital mortality, with a progressive increase in the adjusted OR with decreasing fibrinogen levels. The association with in-hospital mortality remained after adjusting for potential confounders Younger age, lower GCS, systolic blood pressure <90 mmHg, chest decompression, penetrating injury, greater ISS, lower pH and temperature were all associated with lower fibrinogen levels. INR was associated with mortality in our study cohort even after adjusting for fibrinogen level.
aPTT, activated partial thromboplastin time; CI, confidence interval; FC, fibrinogen concentrate; FFP, fresh frozen plasmaINR, international normalised ratio; IQR, interquartile range; N/A, not applicable; NR, not reported; OR, odds ratio; PLT, platelet; RBC, red blood cells; * After adjusting for age, gender, ISS, injury type, pH, temperature, Glasgow Coma Score (GCS), initial international normalised ratio and platelet count

STUDY DETAILS: McQuilten 2017b			
Citation			
McQuilten ZK., Bailey M., Cameron PA., Standworth SJ., Venardos K., Wood EM., Cooper DJ. Fibrinogen concentration and use of fibrinogen supplementation with cryoprecipitate in patients with critical bleeding receiving massive transfusion: a bi-national cohort study. *British Journal of Haematology,* 2017, 179, 131–141. doi: 10.1111/bjh.14804.			
Affiliation/Source of funds			
Author affiliations: Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Transfusion Research Unit, Department of Epidemiology and Preventive Medicine, Monash University, Monash Health Melbourne Australia and NHS Blood and Transplant/Oxford University Hospitals NHS Trust, John Radcliffe Hospital, and Radcliffe Department of Medicine, University of Oxford, Oxford, UK Conflict of interest: The authors have no conflict of interest to disclose. Funding: ZM is supported through a National Health and Medical Research Council (NHMRC) Early Career Fellowship (APP1111485).			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort	III-3	20 hospitals across Australia, New Zealand (ANZ trauma registry)	Hospital
Prognostic factor		**Comparator**	
Fibrinogen concentration		N/A	
Population characteristics			
3566 patients aged ≥ 18 years of age who received massive transfusion (≥ 5 units of RBC within any 4 hour period during admission). Of these, 2829 patients (79%) had fibrinogen levels recorded at the time of massive transfusion.			
Length of follow-up		**Outcomes measured**	
Between April 2011 and October 2015.		Mortality Transfusion volume (RBC, FFP, PLT, Cryoprecipitate or FC)	
Method of analysis			
Association between plasma fibrinogen concentration and in-hospital mortality was modelled by multiple logistic regression analysis. Variables considered for inclusion in the model were hospital, age, gender, clinical context, CCI, Hb, platelet count, APTT, INR and base excess at massive transfusion commencement.			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Moderate Description: The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial.			

STUDY DETAILS: McQuilten 2017b				
RESULTS				
Outcome	**[intervention] n/N (%) median (IQR)**	**[comparator] n/N (%) median (IQR)**	**Risk estimate (95% CI)**	***Statistical significance* *p*-value Heterogeneity[a] I^2 (*p*-value)**
Fibrinogen concentration (<1 g/L, 1.0 to 1.9 g/L, >4 g/L FC versus 2 to 4 g/L)				
Mortality N = 2829 <1 g/L 1.0-1.9 g/L >4 g/L <1 g/L 1.0-1.9 g/L >4 g/L	<1 g/L: 91/198 (46) 1.0-1.5 g/L: 163/622 (26) 1.6-1.9 g/L: 103/532 (19) >4 g/L: 56/244 (23)	2-4 g/L (reference) 200/1233 (16)	Unadjusted OR OR 4.39 (3.20, 6.04) OR 1.55 (1.26, 1.90) OR: 1.54 (1.10, 2.15) Adjusted OR: <1 g/L: OR 2.31 (1.48, 3.60) 1.0-1.9 g/L: OR 1.29 (0.99, 1.67) >4 g/L: OR 2.03 (1.35, 3.04)	Unadjusted: *p* < 0.001 *p* < 0.001 *p* = 0.012 Adjusted: *p* < 0.001 *p* = 0.056 *p* = 0.001
RBC transfused at 24 hours, units N = 2829	<1 g/L: 11 (8, 18) 1.0-1.9 g/L: 9 (7, 13) >4 g/L: 7 (6, 9)	2-4 g/L (reference) 8 (6, 11)	NR	*p* < 0.001
FFP transfused at 24 hours, units N = 2829	<1 g/L: 8 (4, 14) 1.0-1.9 g/L: 6 (4, 10) >4 g/L: 4 (2, 6)	2-4 g/L (reference) 5 (3, 8)	NR	*p* < 0.001
PLT transfused at 24 hours, adult patient dose N = 2829	<1 g/L: 2 (1, 4) 1.0-1.9 g/L: 2 (1, 3) >4 g/L: 0 (0, 1)	2-4 g/L (reference) 1 (0, 2)	NR	*p* < 0.001
Cryoprecipitate or FC transfused at 24 hours,	<1 g/L: 4.2 (2.1, 8.5) 1.0-1.9 g/L: 3.8 (0, 6.8) >4 g/L: 0.0 (0.0, 1.9)	2-4 g/L (reference) 1.7 (0.0, 4.2)	NR	*p* < 0.001
Base deficit (–29 to –8.7, –8.6 to –5, –4.9 to –1.5 versus ≥ –1.4)				
Mortality N = 2829 –29 to –8.7 –8.6 to –5 –4.9 to –1.5 –29 to –8.7 –8.6 to –5 –4.9 to –1.5	NR	NR	Unadjusted OR: OR 4.82 (3.65, 6.35) OR 1.29 (0.95, 1.76) OR 0.89 (0.65, 1.25) Adjusted OR: OR 3.68 (2.70, 5.03) OR 1.33 (0.95, 1.86) OR 0.94 (0.66, 1.33)	Unadjusted: *p* < 0.001 *p* = 0.10 *p* = 0.52 Adjusted: *p* < 0.001 *p* = 0.10 *p* = 0.72
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. The study was conducted in Australia and New Zealand.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context. The study was conducted in Australia and New Zealand.				
Additional comments				
Authors conclusions: After adjustment, fibrinogen < 1 g/L and > 4 g/L remained independently associated with survival.				

STUDY DETAILS: McQuilten 2017b
Lower fibrinogen concentrations were associated with increased mortality after adjusting for clinical context, co-morbidities and other laboratory parameters, but, in addition, higher fibrinogen concentrations were also identified as being linked with mortality risk.

aPTT, activated partial thromboplastin time; CCI, Charlson co-morbidity index; CI, confidence interval; FC, fibrinogen concentrate; FFP, fresh frozen plasma; hB, haemoglobin; INR, international normalised ratio; IQR, interquartile range; N/A, not applicable; NHS, National Health Service; NR, not reported; OR, odds ratio; PLT, platelet; RBC, red blood cells; UK, United Kingdom

Single-arm analysis of RCT

STUDY DETAILS: Moore 2020			
Citation			
Moore HB, Tessmer MT, Moore EE, Sperry JL, Cohan MJ, Chapman MP, Pusateri AE, Guyette FX, Brown JB, Neal MB, Zuckerbraun B, Sauaia A. 2020. Forgot calcium? Admission ionized-calcium in two civilian randomized controlled trials of prehospital plasma for traumatic hemorrhagic shock. *Journal of Trauma and Acute Care Surgery 88*(5), 588-596. doi: 10.1097/TA.0000000000002614			
Affiliation/Source of funds			
The study was funded by the Department of Defense, US Army Medical Research and Materiel Command. Moore EE and Sauaia A were partially funded through the National Institute of General Medical Sciences. *Author affiliations:* Moore EE affiliated with Haemonetics/Instrumentation Laboratory/Stage, Grants. Neal MB affiliated with Janssen Pharmaceuticals/CSL, Behring/Haemonetics. Sauaia A affiliated with Haemonetics. The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
MA of 2 randomised controlled trials (PAMPer and COMBAT)	II	PAMPer (Sperry 2018): Pittsburgh COMBAT (Moore 2018): Denver, Colorado	2 trauma centres
Intervention		**Comparator**	
Hypocalcaemia (i-Ca ≤ 1.0 mmol/L)		Normocalcaemia (i-Ca >1.0 mmol/L)	
Population characteristics			
Adults with traumatic haemorrhagic shock (SBP ≤ 70mmHg or 71-90 mmHg + HR ≥ 108 bpm) enrolled in the University of Pittsburgh Medical Centre (PAMPer trial) or COMBAT trial. Patients had blunt or penetrating injuries for whom i-Ca was collected before calcium supplementation.			
Length of follow-up		**Outcomes measured**	
Only patients enrolled in the University of Pittsburgh Medical Centre in PAMPer were included in the analysis. The authors were unable to obtain i-Ca levels from the other facilities participating in PAMPer.		Mortality Transfusion requirements	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: High *Description:* The study has plausible bias that raises some doubt about the results.			
RESULTS			
Population analysed	**Intervention**	**Comparator**	
Randomised	70	90	
Efficacy analysis (ITT)	70	90	
Efficacy analysis (PP)	70	90	
Safety analysis	70	90	

Outcome	**Intervention n/N (%) Mean ± SD**	**Comparator n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
Hypocalcaemia (i-Ca, ≤1.0 mmol/L) vs normocalcaemia (i-Ca, >1.0 mmol/L)				
Mortality N = 160	13/70 (18.6)	11/90 (12.2)	NR	*No significant difference* *p* = 0.26
	Hypocalcaemia independently associated with survival after adjustment for confounders (age, ISS, Shock index)		HR (1.02, 1.13)	*p* = 0.01
RBC transfusion in 24 hours, units N = 160	5 (2-10) (n = 70)	1 (0-5) (n = 90)	NR	*Favours normocalcaemia* *p* = 0.0002

STUDY DETAILS: Moore 2020				
Plasma transfusion in 24 hours, units N = 160	2 (1-7) (n = 70)	2 (0-4) (n = 90)	NR	*Favours normocalcaemia* *p* = 0.007
Platelet transfusion in 24 hours, units N = 160	0 (0-1) (n = 70)	0 (0-0) (n = 90)	NR	*No significant difference* *p* = 0.30
Cryoprecipitate transfusion in 24 hours, units N = 160	0 (0-0) (n = 70)	0 (0-0) (n = 90)	NR	*Favours normocalcaemia* *p* = 0.0003
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. The study population consisted of patients with both blunt and penetrating trauma which reflects the Australian trauma population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. The studies were performed in the US which has a different health care system to Australia.				
Additional comments				
Authors conclusions: In summary, trauma patients resuscitated with prehospital plasma often present to the hospital with hypocalcaemia, which place them at increased risk of mortality. Citrate in the plasma contributes to hypocalcaemia, but other causes of low i-Ca remain unclear because some patients who did not receive plasma also had hypocalcaemia. Thus, further research into the mechanisms of postinjury hypocalcaemia and associated mortality is needed.				
CI, confidence interval; i-Ca, ionised calcium; ITT, intent to treat; MA; meta-analysis; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; US, United States				

STUDY DETAILS: Lester 2019
Citation
Lester, ELW., Fox, EE., Holcomb, JB., Brasel, KJ., Bulger, EM., Cohen, MJ., Cotton, BA., Fabian, TC., Kerby, JD., O'Keefe, T., Rizoli, SB., Scalea, TM., Schreiber, MA. & Inaba, K. 2019. The impact of hypothermia on outcomes in massively transfused patients. *Journal of Trauma and Acute Care Surgery, 86*(3). 458-463. doi: 10.1097/TA.0000000000002144
Affiliation/Source of funds
Details on funding not provided. The authors declared no conflicts of interest. *Author affiliations:* The Division of General Surgery Department of Surgery, University of Alberta, Edmonton, Alberta, Canada (E.L.W.L.)., Center for Translational Injury Research Division of Acute Care Surgery, Department of Surgery, Medical School, University of Texas Health Science Center, Houston, Texas (E.E.F., J.H.)., Division of Trauma Critical Care and Acute Care Surgery, School of Medicine, Oregon Health and Science University, Portland, Oregon (K.B.)., Division of Trauma and Critical Care Department of Surgery, School of Medicine, University of Washington, Seattle, Washington (E.M.B.)., Department of Surgery University of Colorado, Denver, Colorado (M.C.)., Center for Translational Injury Research Division of Acute Care Surgery, Department of Surgery, Medical School, University of Texas Health Science Center, Houston, Texas (B.A.C.)., Division of Trauma and Surgical Critical Care Department of Surgery, College of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee (T.C.T.C.F.)., Division of Trauma Burns and Surgical Critical Care, Department of Surgery, School of Medicine, University of Alabama, Birmingham, Alabama (J.D.K.)., Division of Trauma Critical Care and Emergency Surgery, Department of Surgery, University of Arizona, Tucson, Arizona (T.O.)., Trauma and Acute Care Service St. Michael's Hospital, Toronto, Ontario, Canada (S.B.R.)., R Adams Crowley Shock Trauma Center University of Maryland, Baltimore, Maryland (T.S.)., Division of Trauma Critical Care and Acute Care Surgery, Department of Surgery, Oregon (M.A.S.). & Health and Science University, Portland, Oregon; and Division of Trauma and Critical Care LAC+USC Medical Center, University of Southern California, Los Angeles, California (K.I.).

STUDY DETAILS: Lester 2019			
Study design	**Level of evidence**	**Location**	**Setting**
Prospective cohort	III-2	USA	Level 1 trauma centres
Prognostic Factor		**Comparator**	
Temperature		not applicable	
Population characteristics			
The population in both intervention groups were predominately male (79% and 84%). Both groups had similar mean ages (39.4, 37.1 years).			
Length of follow-up		**Outcomes measured**	
Patients were followed up after 6 hours, 24 hours and 30 days		Transfusion volume, mortality	
Method of analysis			
STATA was used to conduct the analysis Backwards stepwise negative binomial regression approach was used to model the RBCs administered while hypothermic or normothermic. Frequency weighting was applied. The fit was tested by plotting the dependant variables against both Poisson and negative binomial distributions, comparing the predicted values from each regression to the recorded values and performing goodness of fit tests. A backwards stepwise logistic regression (removal criteria, $p > 0.05$) was performed to determine the adjusted odds ratios (ORs) of 24-hour and 30-day mortality for patients presenting with hypothermia on initial measurement. The ORs were adjusted for the following covariates: number of RBC units used in 24 hours, need for emergent OR (within 90 minutes of arrival), ISS, mechanism of injury (blunt versus penetrating), weight, age, sex, and initial pulse and systolic blood pressure on arrival was assessed and modelled accordingly. The area under the receiver operating characteristic curve was calculated. The analysis was conducted using STATA (version 13; College Station, TX).			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has some important problems and cannot be considered comparable to a well-performed randomised trial.			
RESULTS			
Population analysed	**Hypothermic**		**Normothermic**
Available	399		187
Analysed	399		187

Outcome	**Hypothermic n/N (%) Mean ± SD**	**Normothermic n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
Temperature				
24 hr Mortality N = 586	NR/399 NR	NR/187 NR	OR 2.7 (1.7, 4.5)	*Favours hypothermia* $p < 0.00$
30 Day Mortality N = 586	NR/399 NR	NR/187 NR	OR 1.8 (1.3, 2.4)	*Favours hypothermia* *p < 0.00*
Blood transfusion (RBCs units in 24 hrs) N = 586	N = 399 9.9 (11.4)	N = 187 6.3 (7.9)	RR 0.90 (0.89, 0.92)	*No significant difference* $p = 0.00$

EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
The evidence is directly generalisable to the Australian population. The study included patients ≥ 15 years of age admitted to a trauma centre. The study population is reflective of the Australian clinical population.
Applicability (relevance of the evidence to the Australian health care system)
The evidence is directly applicable to the Australian healthcare context with few caveats. The study was performed in the USA.

STUDY DETAILS: Lester 2019
Additional comments
Authors conclusions: Hypothermia is associated with an increase in blood product consumption and is an independent predictor of mortality

CI, confidence interval; ISS, injury severity score; NA, not applicable; NR, not reported; OR, Odds Ratio; RBCs, Red Blood Cells; RR, Relative Risk; SD, standard deviation; USA, United States of America

E2 Massive haemorrhage protocol (Question 2)

Systematic reviews/meta-analyses

STUDY DETAILS: Vogt 2012			
Citation			
Vogt, K. N., Van Koughnett, J. A., Dubois, L., Gray, D. K. and Parry, N. G. (2012), The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis*. Transfusion Medicine, 22: 156-166. doi:10.1111/j.1365-3148.2012.01150.x			
Affiliation/Source of funds			
The study did not receive funding or support in any manner. *Author affiliations*: The primary author of the review was also the primary author of one of the included studies. Hence all assessments for this study were completed by two other authors. Department of Surgery, Schulich School of Medicine & Dentistry, University of Western Ontario (K.N.V, J.V.K, L.D, D.K.G, & N.G.P). Trauma Program, London Health Sciences Centre, (D.K.G, & N.G.P). Centre for Critical Illness Research (N.G.P). Division of Critical Care, London Health Sciences Centre, London, Ontario, Canada (N.G.P)			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of observational studies	I-III	5 studies in USA 1 in Canada 1 in Denmark	Civilian trauma centres (hospitals)
Intervention		**Comparator**	
Blood products delivered through the use of a formal trauma transfusion pathway (TTP)		Blood products delivered without the use of a formal trauma transfusion pathway (TTP)	
Population characteristics			
Adult patients requiring massive transfusion due to civilian trauma Included 7 observational studies that compared trauma patients requiring massive transfusion (MT) through the use of a formal Trauma Transfusion Protocol (TTP) with a retrospective cohort of patients requiring MT prior to the introduction of a TTP			
Length of follow-up		**Outcomes measured**	
Citations published between 1980 and 2011		Mortality, indices of coagulation, Amount of blood component products transfused, Complications	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The overall risk of bias for all included studies was judged by the review authors to be high, primarily due to a lack of adequate adjustment for confounding, and the universal use of retrospective controls.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**TTP** **n/N (%)** **Mean ± SD**	**No TTP** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TTP versus control				
30-day or in-hospital mortality N = 1801 (6 studies)	NR	NR	RR 0.69 (0.55, 0.87)	*Favours TTP* *p* = 0.001 Moderate heterogeneity I^2 = 49% (*p* = 0.08)
Adjusted estimate [b] Cotton 2008	48/94 (51.1)	77/117 (65.8)	RR 0.51 (0.29, 0.90)	*p* = 0.02
Unadjusted estimate (5 studies)	NR	NR	RR 0.72 (0.56, 0.91)	*p* = 0.001 Moderate heterogeneity

STUDY DETAILS: Vogt 2012				
Dente 2009 Johansson 2009 O'Keefe 2008 Riskin 2009 Vogt 2009	25/73 (34.2) 17/50 (34) NR NR NR	46/84 (55) 46/82 (56) NR NR NR	RR 0.69 (0.52, 0.91) RR 0.65 (0.51, 0.82) RR 1.05 (0.77, 1.44) RR 0.42 (0.20, 0.90) RR 0.64 (0.32, 1.27)	I^2 = 49% (*p* = 0.08)
Multi-organ failure Cotton 2009	NR	NR	OR 0.20 (0.11, 0.39)	*Favours TTP* *p* = NR
Sepsis Cotton 2009	NR	NR	OR 0.43 (0.21, 0.88)	*Favours TTP* *p* = NR
Blood component use (24 hrs, PRBC) N = 1267 (3 studies) Cotton 2008 Johansson 2009 Vogt 2009	NR 18.8 ± 11.2 (94) 18 ± 12.6 (442) 23 ± 10.7 (23)	NR 19.8 ± 11.2 (117) 19.2 ± 15.8 (390) 25 ± 15.2 (23)	MD –1.17 (–2.70, 0.36) MD 0.00 (–3.04, 3.04) MD –1.20 (–3.16, 0.76) MD –2.00 (–9.60, 5.60)	*No significant difference* *p* = 0.27 No significant heterogeneity I^2 = 0% (*p* = 0.78)
Blood component use (24 hrs, FFP) N = 1089 (3 studies) Cotton 2008 Johansson 2009 Vogt 2009	NR 9.9 ± 7 (94) 13.5 ± 12.3 (442) 14 ± 8 (23)	NR 12.4 ± 12.5 (117) 12.1 ± 15.2 (390) 15 ± 10.1 (23)	RR –0.50 (–3.37, 2.37) RR –2.50 (–5.17, 0.17) RR 1.40 (–0.49, 3.29) RR –1.00 (–6.27, 4.27)	*Favours TTP* *p* = 0.22 No significant heterogeneity I^2 = 0% (*p* = 0.06)
Blood component use (24 hrs, PLT) N = 435 (3 studies) Cotton 2008 Johansson 2009 Vogt 2009	NR 31 ± NR (94) 5.0 ± NR (442) 3 ± NR (23)	NR 6.8 ± NR (117) 1.7 ± NR (46) 2 ± NR (23)	NR	NR
Blood component use (PRBC, overall) N = 77 (1 study) Riskin 2009	23.9	20.5	NR	*Favours TTP*
Blood component use (FFP, overall) N = 77 (1 study) Riskin 2009	12.3	10.7	NR	*Favours TTP*
Blood component use (PLT, overall) N = 77 (1 study) Riskin 2009	2.3	2.8	NR	*Favours no TTP*
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats, (depending on the differences in TTP used in Australia).				
Additional comments				
Authors conclusions: The authors concluded that the use of TTPs appears to be associated with a reduction in mortality amongst trauma patients requiring MT without a clinically significant increase in the number of PRBC transfused and a potential reduction in plasma transfusion. A RCT is required to provide higher-level evidence. *Included studies:*				

STUDY DETAILS: Vogt 2012
Cotton 2008, Cotton 2009, Dente 2009, Johansson 2009, O'Keefe 2008, Riskin 2009, Vogt 2009

CI, confidence interval; ITT, intention-to-treat; MD, mean difference; MT, massive transfusion; NR, no result; OR, odds ratio; PLT, platelets; PP, per-protocol; PRBC, packed red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TTP, trauma transfusion pathway

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Adjusted for age, gender, mechanism of injury, TRISS, and 24-hour transfusion requirements

STUDY DETAILS: Mitra 2013			
Citation			
Mitra, B., O'Reilly, G., Cameron, P. A., Zatta, A. and Gruen, R. L. (2013), Effectiveness of MTP on mortality. ANZ J Surg, 83: 918-923. doi:10.1111/ans.12417			
Affiliation/Source of funds			
Details on funding or potential conflicts of interest not provided. *Author affiliation*: The Alfred Hospital, Australia (B.M., G.O., P.A.C. & R.L.G.); Monash University, Australia (B.M., G. O., P.A.C. & A.Z.)			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of observational studies	I-III	Australia	Single Centre, trauma
Intervention		**Comparator**	
After institutional massive transfusion protocol was implemented (post-MTP)		Pre-MTP	
Population characteristics			
Adult trauma patients in the initial trauma ResusCitation phase Mean mortality pre-MTP was 41.3% (SD 13.1) All observational studies that compared patients in the same institution in a period prior to the implementation of an MTP			
Length of follow-up		**Outcomes measured**	
Citations published between 1990 and June 2013		In-hospital or short-term mortality Change in transfusion practice identified by a change in transfusion ratios or volume of PRBCs and the usage of PRBCs and FFP	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The review authors did not make a judgement on the overall risk of bias for included studies. It was mentioned that only 1 out of 8 included studies (Shaz 2010) used prospectively collected data in the intervention group. Baseline demographics was comparable across the group except for Cotton 2009 (higher ISS score) and Simmons 2010 (higher Hb).			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**Post-MTP** **n/N (%)** **Mean ± SD**	**Pre-MTP** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Post-MTP versus pre-MTP				
Mortality at 30 days N = 1586 (8 studies)	NR	NR	Pooled OR 0.73 (0.48, 1.11)	*No significant difference* *p* = 0.14 Substantial heterogeneity I2 = 63.8% (*p* = 0.007)
Riskin 2009 (N = 77)	7/37 (19)	18/40 (45)	OR 0.29 (0.10, 0.80)	
Cotton 2009 (N = 264)	54/125 (43.2)	88/141 (62.4)	OR 0.32 (0.19, 0.52)	

STUDY DETAILS: Mitra 2013				
O'Keefe 2008 (N = 178) Shaz 2010 (N = 224) Simmons 2010 (N = 777) Dirks 2010 (N = 66) Sisak 2012 (N = 58) Sinha 2013 (N = 152)	69/132 (52.3) 63/132 (47.7) 81/426 (19.0) 47/156 (30.1) 13/28 (46.4) 24/83 (28.9)	23/46 (50) 42/84 (50) 84/351 (23.9) 24/97 (24.7) 12/30 (40) 16/69 (23.2)	OR 1.10 (0.56, 2.14) OR 1.10 (0.63, 1.89) OR 0.75 (0.53, 1.05) OR 1.21 (0.41, 3.61) OR 1.30 (0.46, 3.68) OR 0.77 (0.16, 3.75)	
Transfusion volumes (intra-operative PRBC, FFP, platelets) Cotton 2009 (N = 264)	NR	NR	NR	*Favours comparator* *p* = NR
Transfusion volumes (post-operative PRBC, FFP, platelets) Cotton 2009 (N = 264)	NR	NR	NR	*Favours intervention* *p* = NR
Transfusion volumes (PRBC) O'Keefe 2008 (N = 178) Riskin 2009 (N = 77) Simmons 2010 (N = 777) Shaz 2010 (N = 224) Dirks 2010 (N = 66) Sisak 2012 (N = 152)	 11.8 ± 11.8 (132) 20.5 ± 2.6 (37) 17 ± 12 (426) 24 ± 14 (132) NR 19.8 ± 8.5 (28)	 15.5 ± 15.5 (46) 23.9 ± 2.7 (40) 19 ± 11 (351) 23 ± 23 (84) NR 19.6 ± 9.7 (30)	 NR NR NR NR NR NR	 *Favours intervention,* *p* = NR *Favours intervention,* *p* = NR *Favours comparator,* *p* = NR No difference, *p* = NR
Transfusion volumes (FFP) Riskin 2009 (N = 77) Sisak 2012 (N = 58) O'Keefe 2008 (N = 178) Simmons 2010 (N = 777) Shaz 2010 (N = 224) Dirks 2010 (N = 66) Sinha 2013 (N = 152)	 10.7 ± NR 9.4 ± 5.8 (132) 5.7 ± 5.4 (132) 8 ± 8 (426) 13 ± 12 (132) NR NR	 12.3 ± NR 8.1 ± 6.2 (30) 8.7 ± 6.9 (46) 14 ± 11 (351) 8 ± 7 (84) NR NR	 NR NR NR NR NR NR NR	 No difference, *p* = NR *Favours intervention,* *p* = NR *Favours comparator,* *p* = NR *Favours comparator,* *p* = NR *Favours comparator,* *p* = NR *Favours comparator,* *p* = NR
Transfusion volumes (PLT) Riskin 2009 (N = 77) Shaz 2010 (N = 224) O'Keefe 2008 (N = 178) Sisak 2012 (N = 58) Dirks 2010 (N = 66) Sinha 2013 (N = 152) Simmons 2010 (N = 777) Dirks 2010 Sinha 2013	 2.3 ± NR 2 ± 2 (132) 1.1 ± NR (132) 10.1 ± 6.5 (28) NR NR 1 ± 2 (426) Median (range) 0 (0-0) 3 (2-4)	 2.8 ± NR 2 ± 1 (84) 1.7 ± NR (46) 5.8 ± 6.8 (30) NR NR 2 ± 3 (351) Median (range) 1 (0-4) 2 (1-3)	 NR NR NR NR NR NR NR NR NR	 No difference, *p* = NR *Favours intervention,* *p* = NR *Favours comparator,* *p* = NR *Favours comparator,* *p* = NR *Favours comparator,* *p* = NR

STUDY DETAILS: Mitra 2013				
				Favours comparator, p = NR p = NR p = NR
Time to delivery of blood products (3 studies) Riskin 2009 (N = 77) O'Keefe 2008 (N = 178) Dirks 2010 (N = 66)	 NR NR NR	 NR NR NR	 NR NR NR	 *Favours intervention,* p = NR *Favours intervention,* p = NR *Favours intervention,* p = NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The review does not provide descriptions of the setting for each included study.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The review does not provide descriptions of the setting for each included study.				
Additional comments				
Authors conclusions: All studies were of low quality with varied definitions, and although involving 1586 trauma patients who underwent massive transfusions, there was no clear demonstration of improved patient outcomes. *Included studies:* Riskin 2009, Cotton 2009, O'Keefe 2008, Shaz 2010, Simmons 2010, Dirks 2010, Sisak 2012, Sinha 2013				

CI, confidence interval; FFP, fresh frozen plasma; Hb, haemoglobin; ISS, injury severity score; ITT, intention-to-treat; MD, mean difference; MTP, massive transfusion protocol; NR, not reported; OR, odds ratio; PLT; platelet, PTL; PP, per-protocol; PRBC, packed red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Cannon 2017			
Citation			
Cannon, J.W., Khan, M.A., Raja, A.S., Cohen, M.J., Como, J.J., Cotton, B.A., Dubose, J.J., Fox, E.E., Inaba, K., Rodriguez, C.J. and Holcomb, J.B., 2017. Damage control ResusCitation in patients with severe traumatic haemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. *Journal of Trauma and Acute Care Surgery*, 82(3), pp.605-617.			
Affiliation/Source of funds			
The author declares no conflict of interest. Author Bryan A. Cotton is a consultant, Haemonetics Corporation. Source of funding not disclosed			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of RCTs and cohort studies	I-III	Not specified	Trauma
Intervention		**Comparator**	
PICO 1: MHP (referred to as MT/DCR)		PICO 1: no MHP	
Population characteristics			
Patients with severe trauma at risk of death from haemorrhage, defined as patients requiring blood transfusions and/or injury severity score greater than 25. PICO 1: 11 retrospective studies			

STUDY DETAILS: Cannon 2017				
(Nascimento 2013, Campion 2014, Duchesne 2010, Cotton 2009, O'Keeffe 2008, Riskin 2009, Shaz 2010, Kahn 2013, Cotton 2011, fox 2008, Cinat 1999)				
Length of follow-up			**Outcomes measured**	
Databases searched: PubMed, Medline, Embase Search dates: Jan 1985 through December 2015			Mortality (in hospital or 30 day) Blood products used (RBC in 24 hours)	
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* Study identified 11 studies for inclusion however only 7 were included in meta-analysis. All included studies were relatively small retrospective studies at serious risk of bias. The outcome of blood products used is at serious risk of inconsistency, indirectness, and imprecision. Study reported study heterogeneity				
RESULTS:				
Outcome **No. trials (No. patients)**	**MHP** **n/N (%)** **Mean ± SD**	**No MHP** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** ***p*-value (I^2)**
MHP/DCR versus no MHP/DCR				
Mortality (In hospital or 30 day) N = 1149 6 retrospective studies Campion 2013 (N = 216) Cotton 2009 (N = 166 Duchesne 2010 (N = 196) O'Keeffe 2008 (N = 178) Riskin 2009 (N = 77) Shaz 2010 (N =216)	239/597 (40.0) 27/99 (27.3) 54/125 (43.2) 19/72 (26.4) 69/132 (52.3) 7/37 (18.9) 63/132 (47.7)	269/552 (48.7) 42/117 (35.9) 88/141 (62.4) 56/124 (45.2) 23/46 (50) 18/40 (45) 42/84 (50)	RR 0.614 (0.43, 0.87) AR 120 fewer per 1000 (from 35 to 197 fewer) 0.67 (0.37, 1.20) 0.46 (0.28, 0.75) 0.44 (0.23, 0.82) 1.10 [0.56, 2.14] 0.29 [0.10, 0.80] 0.91 [0.53, 1.58]	*Favours intervention* *p* = 0.006 Moderate heterogeneity I^2 = 48% (*p* = 0.09)
Blood products used (units of RBC/24 hours) N = 511 4 retrospective studies Fox 2008 (N = 40) O'Keeffe 2008 (N = 178) Riskin 2009 (N = 77) Shaz 2010 (N = 216)	(n = 317) 23 ± 18 (16) 11.8 ± 11.8 (132) 20.5 ± 2.6 (37) 24 ± 14 (132)	(n = 194) 12 ± 6.4 (24) 15.5 ± 15.5 (46) 23.9 ± 2.7 (40) 23 ± 14 (84)	MD –0.36 (–4.54, 3.83) 11.00 [1.82, 20.18] –3.70 [–8.61, 1.21] –3.40 [–4.58, –2.22] 1.00 [–4.54, 3.83]	No significant *difference* *p* = 0.87 Substantial heterogeneity I^2 = 78% (*p* = 0.004)
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
Overall, study population is generalisable to the guideline's population. Fox 2008 was conducted in military patients and results may not be generalisable to the greater population, particularly the outcome of blood products used.				
Applicability (relevance of the evidence to the Australian health care system)				
Study is applicable to the Australian health care system. Except for the Fox 2008 study which was conducted in a military hospital, other included studies were conducted in civilian hospitals. Considerable variability in the MTPs described in terms of products provided and ratios.				
Additional comments				
Authors conclusions In adult patients with severe trauma, we recommend the use of a massive transfusion/damage control resuscitation protocol in comparison to no protocol to reduce mortality. *Included studies*				

STUDY DETAILS: Cannon 2017
Nascimento 2013, Campion 2014, Duchesne 2010, Cotton 2009, O'Keeffe 2008, Riskin 2009, Shaz 2010, Kahn 2013, Cotton 2011, Fox 2008, Cinat 1999

AR, absolute risk; CI, confidence interval; DCR; damage control resuscitation; ITT, intention-to-treat; MD, mean difference; MHP; Major haemorrhage protocol; MT, major transfusion; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

STUDY DETAILS: Maw 2018			
Citation			
Maw, G., Furyk C., 2018. Pediatric Massive Transfusion. A Systematic Review. Pediatr Emer Care, 34, pp.594-598.			
Affiliation/Source of funds			
The authors declare no conflict of interest. The authors are affiliated with the Australasian College for Emergency Medicine (G.M.); and Australian and New Zealand College of Anaesthetists (C.F.) in Melbourne, Australia.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of nonrandomised trials including 3 retrospective analyses and one non-randomised prospective study	I-III	US, Iraq and Afghanistan	Trauma, surgical
Intervention		**Comparator**	
Chidester 2012 – uncrossmatched blood via MTP Hendrickson 2012 - MTP designed for 5 different weight ranges Nosanov 2013 – low, medium or high ratios of platelets to RBCs Edwards 2015 – higher doses of FFP to RBCs and high volume of crystalloid		Chidester 2012 – uncrossmatched blood at physician discretion Hendrickson 2012 - Blood products at physician discretion (not described) Nosanov 2013 – low, medium or high ratios of plasma to RBCs Edwards 2015 – comparison at varying doses	
Population characteristics			
Paediatric patients (<18 years) with traumatic injury requiring blood transfusion *Relevant to this review* Chidester 2012 –prospective cohort study (N = 55, duration 2009-2011) of paediatric patients with trauma or surgical haemorrhage requiring blood transfusion Hendrickson 2012 – retrospective cohort study with before and after (N = 102) of paediatric patients with traumatic haemorrhage *Not relevant to Question 2 (not MTP vs no MTP)* Nosanov 2013 – retrospective analysis (N = 105) of paediatric trauma patients Edwards 2015 – retrospective analysis (N = 77) requiring massive transfusion) of paediatric patients trauma patients			
Length of follow-up		**Outcomes measured**	
Databases searched: Cochrane Central Register of Controlled Trials, Medline, EMBASE, Web of Science, the Joanna Briggs Institute EBP Database, CINAHL, AUSTHealth, grey literature by google search, clinical trial registries, relevant conference proceedings, hand search of reference lists from key trials Search date: No restrictions on dates or language with the search run on February 29, 2016		30-day mortality Unnecessary transfusion including morbidity and waste Avoidable complications including ICU days and ventilator days	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* All four included studies were of very low quality. This assessment was based mainly on high risk of selection bias and lack of allocation concealment.			

STUDY DETAILS: Maw 2018				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
MTP versus No MTP				
Mortality (to hospital discharge) Hendrickson 2012 (n = 102) Chidester 2012 (n = 55)	 20/53 (38) 15/33 (45)	 11/49 (23) 10/22 (45)	 NR NR	 *No significant difference* *No significant difference*
Ventilator days Hendrickson 2012 (n = 102)	 Median = 2 days	 Median = 6 days	 NR	 NR
ICU days Hendrickson 2012 (n = 102)	 Median = 7 days (n = 53)	 Median = 9 days (n = 49)	 NR	 NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. Edwards 2015 was a retrospective review of 1300 injured children presenting to US military hospitals in Afghanistan and Iraq via a trauma database.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context. The reviewer's state there is variability in the definition of massive transfusion in children. Additionally, the definition of MTP used in the studies in not clear.				
Additional comments				
Authors conclusions: There is little evidence for improved outcomes using component-based transfusion in a rigid 1:1:1 strategy in children. A goal-directed approach using viscoelastic haemostatic assay–guided treatment with early institution of tranexamic acid and fibrinogen replacement is considered the way forward. This recommendation is based upon very low-quality evidence. *Included studies:* Hendrickson 2012, Chidester 2012, Edwards 2015, Nosanov 2013 21 further articles were deemed relevant but are not listed individually.				

CI, confidence interval; Coh, cohort; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; MD, mean difference; MTP, massive transfusion protocol; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic reveiw

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Sommer 2019			
Citation			
Sommer, N., B. Schnüriger, D. Candinas and T. Haltmeier (2019). "Massive transfusion protocols in non-trauma patients: A systematic review and meta-analysis." *Journal of Trauma and Acute Care Surgery* 86(3): 493-504.			
Affiliation/Source of funds			
The authors declared no conflicts of interest or financial ties.			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of observational studies	I-III (included all retrospective studies)	NR all single centre studies except Chay 2016, which was a multicentre study	Mixed trauma and non-trauma Non-trauma patients including: Perioperative Gastrointestinal bleeding Obstetric Vascular emergencies

STUDY DETAILS: Sommer 2019	
Intervention	**Comparator**
Massive transfusion protocol (MTP)	Non-MTP (off protocol)
Population characteristics	
Adult (18 years or older) non-trauma patients with massive bleeding 12 included studies with 2475 patients in total and 1620 non-trauma patients, majority male (64.4 to 87.1%) except studies with obstetric patients only. Age 29.9 to 73.0 years *7 studies included both trauma and non-trauma patients:* Bauman Kreuziger 2014: 50% trauma, 18% vascular rupture, 13% GI bleeding, 9% cardiothoracic surgery, 4% obstetric, 1.6% thrombosis, 1% orthopaedic, 4% other Balvers 2015: 63% surgery, 13% internal Medicine, 11% other, 9% trauma, 4% obstetric Chay 2016: 39% trauma, 30% major surgery, 25% GI bleeding, 6% obstetric, McDaniel 2013: 61% trauma, 13% GI bleeding, 4% medical bleeding, 11% postsurgical/procedural complications, 11% vascular emergencies, 0.6% cerebral haemorrhage Morse 2012: 92% trauma, 4% GI bleeding, 3% intraoperative bleeding, 15 obstetrics, 0.2% ruptured AAA Sinha 2013: 24% trauma, 20% ruptured AAA, 19% surgery other than cardiac, 15% GI bleeding, 11% obstetrics, 8% cardiac surgery, 3% liver transplantation Wijaya 2016: 61% trauma, 26% GI bleeding, 6.5% ruptured AAA, 2% ruptured splenic artery aneurysm 2% intraoperative bleeding, 2% postoperative bleeding *5 studies included non-trauma patients only:* Dutta 2017: 100% obstetric Goodnough 2011: 100% obstetric Gutierrez 2012: 100% obstetric Johansson 2007: 100% ruptured AAA Martinez-Calle 2016: 29% oncologic surgery, 34.5% cardiovascular surgery, 19% other surgery, 18% nonsurgical bleeding	
Length of follow-up	**Outcomes measured**
All included studies were published between 2007 and 2017. However, this was not stated as a pre-specified search filter. Searched PubMed only.	24-hour mortality 30-day mortality Blood product transfusion including number of packs and transfusion ratios Wastage of blood products Overactivation of MTP (proportion of patients with MTP activation who received <10 units of PRBC)
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* Overall, the review authors considered the quality of included studies to be fair to poor. Three studies analysed a mixed cohort of non-trauma and trauma patients. None of the included studies used a matched Study design or adjusted for confounders.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**MTP** **n/N (%)** **Mean ± SD**	**Non-MTP** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
MTP versus non-MTP				
24-hour mortality N = 430 (3 studies in meta-analysis)	9/257	13/173	OR 0.42 (0.01, 16.62)	*No significant difference* *p* = 0.65 Substantial heterogeneity
McDaniel 2013	8/26 (30.8)	6/38 (15.8)	OR 2.37 (0.71, 7.92)	I^2 = 89% (*p* = 0.002)
Martinez 2016	1/208 (0.5)	7/96 (7.3)	OR 0.06 (0.01, 0.51)	

STUDY DETAILS: Sommer 2019				
Dutta 2017	0/23 (0)	0/39 (0)	Not estimable	
Chay 2016	52/347 (15.0)	23/192 (12.0)	1.22 (0.77, 1.93)	*p* = 0.386
Wijaya 2016	NR	NR		
Balvers 2015	52/355 (15)	23/192 (12)		
B-Kreuziger 2014	NR	NR		
Sinha 2013	NR	NR		
Morse 2012	15/37 (41.0%)	NA		
Gutierrez 2012	NR	NR		
Goodnough 2011	NR	NR		
Johansson 2007	NR	NR		
30-day mortality N = 562 (4 Coh)	63/307	91/255	OR 0.56 (0.30, 1.07)	*No significant difference* *p* = 0.08 Moderate heterogeneity
Johansson 2007	17/50 (34)	46/82 (56)	OR 0.40 (0.19, 0.84)	I^2 = 55% (*p* = 0.11)
McDaniel 2013	13/26 (50.0)	16/38 (42.1)	OR 1.38 (0.50, 3.75)	
Martinez-Calle 2016	33/208 (15.9)	29/96 (30.2)	OR 0.44 (0.25, 0.77)	
Dutta 2017	0/23 (0)	0/39 (0)	Not estimable	
Balvers 2015	124/355 (35)	65/192 (34)	1.03 (0.81, 1.32)	*p* = 0.801
Chay 2016	NR	NR		
Wijaya 2016	NR	NR		
B-Kreuziger 2014	NR	NR		
Sinha 2013	NR	NR		
Morse 2012	18 (49.0)	NA		
Gutierrez 2012	NR	NR		
Goodnough 2011	NR	NR		
PRBC transfusion volume, Units	Median (IQR)	Median (IQR)		
Dutta 2017	7 (5–9) (n = 23)	6 (5–8) (n = 39)	NR	*No difference, p* = 0.85
Martinez-Calle 2016	12 (8–13), 10 (8–12)	9 (8–14)	NR [b]	*No difference, p* = 0.963
Balvers 2015	8 (7–13) (n=355)	8 (6–12) (n = 192)	NR	*No difference, p* = 0.279
Sinha 2013	14 (11–21) (n=83)	16 (12–20) (n = 69)	NR	NR
Johansson 2007 (operating room)	NR	NR	NR	*No difference*, NR
Johansson 2007 (intensive care unit)	2 (0–30)	6 (0–54)	NR	*Favours MTP, p* < 0.05
	Mean	Mean		
McDaniel 2013	12.6 ± 11.5 (n = 26)	12.2 ± 9.0 (n = 38)	NR	*No difference, p* = 0.864
FFP transfusion volume, units	Median (IQR)	Median (IQR)		
Dutta 2017	2 (0–4)	4 (1–5)	NR	*No difference, p* = 0.28
Martinez 2016	5(4–9), 5 (3–9)	5 (3–9)	NR	*No difference, p* = 0.376
Balvers 2015	6 (4–11)	6 (3–9)	NR	*No difference, p* = 0.224
Sinha 2013	10 (7–17)	6 (5–10)	NR	NR
Johansson 2007 (operating room)	4 (2–16)	0 (0–3)	NR	*Favours non-MTP, p* < 0.05
Johansson 2007 (intensive care unit)	0 (0–4)	1 (0–6)	NR	*Favours MTP, p* < 0.05
	Mean	Mean		
McDaniel 2013	9.2 ± 8.0 (n = 26)	8.9 ± 8.7 (n = 38)	NR	*No difference, p* = 0.631

STUDY DETAILS: Sommer 2019				
PLT transfusion volume, units	Median (IQR)	Median (IQR)		
Dutta 2017	0 (0–0.6)	0 (0–0.6)	NR	*No difference, p* = 0.63
Martinez 2016	1 (0–2), 1 (0–2)	1 (0–2	NR	*No difference, p* = 0.751
Balvers 2015	2 (0–4)	2 (1–3)	NR	*No difference, p* = 0.139
Sinha 2013	3 (2–4)	2 (1–3)	NR	NR
Johansson 2007 (operating room)	11 (2–42)	7 (0–46)	NR	*Favours non-MTP, p* < 0.05
Johansson 2007 (intensive care unit)	2 (0–12)	4 (0–32)	NR	*Favours MTP, p* < 0.05
	Mean	Mean		
McDaniel 2013	7.2 ± 6.7 (n = 26)	6.5 ± 8.6 (n = 38)	NR	*No difference, p* = 0.183
Wastage of pRBC				*No significant difference*
McDaniel 2013	3/613 (0.5)	3/848 (0.35)	1.38 (0.28, 6.83)	*p* = 0.700
Wastage of FFP				*No significant difference*
McDaniel 2013	1/406 (0.25)	4/553 (0.72)	0.34 (0.04, 3.04)	*p* = 0.403
Wastage of PLT				*Favours non-MTP*
McDaniel 2013	39/304 (12.8)	29/358 (8.1)	1.58 (1.00, 2.50)	*p* = 0.46
FFP time to delivery, minutes	Median (IQR)	Median (IQR)	NR	*Favours MTP*
McDaniel 2013	1.0 (0.0-2.0)	8.0 (0.0-37.5)		*p* = 0.009
PLT time to delivery, minutes	Median (IQR)	Median (IQR)	NR	*Favours MTP*
McDaniel 2013	7.0 (0.0-15.0)	24.0 (9.0-96.0)		*p* = 0.010
Overactivation of MTP				
Wijaya 2016	28/46 (60.8)	NA	NA	*NA*
B- Kreuziger 2014	41/63 (65)	NA		
McDaniel 2013	14/26 (53.8)	NA		
Morse 2012	20/37 (54)	NA		
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats, depending on the differences in TTP used in Australia.				
Additional comments				
Authors conclusions: The review authors conclude that there is limited evidence that the implementation of MTP may be associated with decreased mortality in non-trauma patients. However, due to the high heterogeneous patient characteristics and definition of MTP in the studies, further prospective investigation is warranted. *List of relevant included studies:* Balvers 2015, Bauman Kreuziger 2014, Chay 2016, Dutta 2017, Goodnough 2011, Gutierrez 2012, Johansson 2007, Martinez 2016, McDaniel 2013, Morse 2012, Sinha 2013, Wijaya 2016				

AAA, abdominal aortic aneurysm; CI, confidence interval; Coh, cohort study; FFP, fresh frozen plasma; GI, gastrointestinal; IQR, interquartile range; ITT, intention-to-treat; MD, mean difference; MTP, massive transfusion protocol; NA, not applicable; NR, not reported; OR, odds ratio; PLT, platelets; PP, per-protocol; PRBC, packed red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. The MTP implemented in Martinez-Calle 2016 was updated during the study period (MTP 1: 2007–2009 and MTP 2: 2010–2012). The *p*-value is pre-MTP vs MTP 1 vs MTP2

STUDY DETAILS: Consunji 2020			
Citation			
Consunji R, Elseed A, El-Menyar A, Sathian B, Rizoli S, Al-Thani H & Peralta R. The effect of massive transfusion protocol implementation on the survival of trauma patients: a systematic review and meta-analysis. Blood Transfusion. 2020; 18: 434-435			
Affiliation/Source of funds			
Details on funding not provided. The authors declared no conflicts of interest. *Author affiliations:* RC, AE, AEM, SR, HAT & RP affiliated with the Department of Surgery, Section of Trauma Surgery, Hamad General Hospital, Doha, Qatar. AEM & BS affiliated with Department of Clinical Research, Hamad General Hospital, Doha, Qatar. AEM affiliated with Clinical Medicine, Weill Cornell Medical College, Doha, Qatar. RP affiliated with Department of Surgery, Universidad Nacional Pedro Henriquez Urena, Santo Domingo, Dominican Republic.			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of observational studies (17)	I-III	Most studies in the US. One study multicentre.	Trauma
Intervention		**Comparator**	
Trauma patients receiving or anticipated to receive massive blood transfusion via MTP		Trauma patients receiving or anticipated to receive massive blood transfusion via no MTP	
Population characteristics			
Cotton 2009, Dirks 2010, Hwang 2018, Nunn 2017, O'Keeffe 2008, Riskin 2009, Shaz 2010, Sinha 2013, Sisak 2012, van der Meij 2019 focused exclusively on civilian patients with haemorrhage requiring massive transfusion. Sinha 2013 included both trauma and non-trauma patients (mortality of trauma reported separately). Simmons 2010 exclusively analysed military personnel with haemorrhage requiring massive transfusion.			
Length of follow-up		**Outcomes measured**	
Databases searched: Medline, PubMed, Google Scholar and Cochrane Library. Citations published between 1 January 2008 and 30 June 2019		Mortality (overall, 24-hour and 30-day)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* All studies were of moderate quality based on GRADE criteria. Risk of bias was reported as not serious for all included studies. There was no evidence of publication bias for the included studies.			
RESULTS:			
Outcome **No. patients** **Trials**	**Post-MTP** **n/N (%)**	**Pre-MTP** **n/N (%)**	**Odds ratio (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Post-MTP versus pre-MTP				
Overall mortality 14 studies; N = 3201	542/1799 (30.1)	542/1402 (38.7)	OR 0.71 (0.56, 0.90)	*Favours intervention* *p* = 0.04 Moderate heterogeneity I^2 = 44%
Brinck 2016	35/206 (16.9)	39/146 (26.5)	OR 0.56 (0.34, 0.94)	*p* = 0.032
Hwang 2018	43/126 (34.1)	35/64 (54.7)	OR 0.48 (0.26, 0.88)	*p* = 0.007
Maciel 2015	9/17 (53)	25/29 (86)	OR 0.23 (0.06, 0.91)	*p* = 0.03
Noorman 2016	10/144 (7)	13/57 (23)	OR 0.25 (0.10, 0.62)	*p* = 0.002
Riskin 2009	7/37 (19)	18/40 (45)	OR 0.29 (0.00, 0.80)	*p* = 0.02
Cotton 2009	54/125 (43.2)	88/141 (62.4)	OR 0.46 (0.28, 0.75)	*p* = 0.185
Dirks 2010	47/156 (30.1)	24/97 (24.7)	OR 1.31 (0.74, 2.33)	*p* = 0.382
O'Keeffe 2008	69/132 (52.3)	23/46 (50.0)	OR 1.10 (0.56, 2.14)	*p* = NR
Nunn 2017	83/208 (40.1)	113/239 (47.2)	OR 0.77 (0.53, 1.12)	*p* = 0.1732

STUDY DETAILS: Consunji 2020				
Shaz 2010	63/132 (48)	42/84 (50)	OR 0.91 (0.53, 1.58)	*p* = 0.47
Simmons 2010	81/426 (19)	84/351 (23.9)	OR 0.75 (0.53, 1.05)	*p* = 0.115
Sinha 2013	24/83 (29)	16/69 (23)	OR 0.77 (0.16, 3.75)	*p* = 0.43
Sisak 2012	13/28 (46)	12/30 (40)	OR 1.30 (0.46, 3.68)	*p* = 0.791
van der Meij 2019	14/47 (29.8)	16/54 (29.6)	OR 1.16 (0.53, 2.58)	*p* = 0.99
24-hour mortality 6 studies; N = 1020	131/608 (21.5)	122/412 (29.6)	OR 0.81 (0.57, 1.14)	*No significant difference* *p* = 0.32 Mild heterogeneity I^2 = 15%
Noorman 2016	3/144 (2)	6/57 (11)	OR 0.18 (0.04, 0.75)	*p* = 0.004
Cotton 2009	39/125 (31)	55/141 (39)	OR 0.71 (0.43, 1.18)	*p* = 0.185
O'Keeffe 2008	27/132 (20.5)	9/46 (19.6)	OR 1.06 (0.46, 2045)	*p* > 0.05
Shaz 2010	38/142 (29)	27/84 (32)	OR 0.85 (0.47, 1.54)	*p* = 0.28
Sisak 2012	10/28 (35.7)	9/30 (30)	OR 1.30 (0.43, 3.89)	*p* = 1.00
van der Meij 2019	14/47 (29.8)	16/54 (29.6)	OR 1.01 (0.43, 2.37)	*p* = 0.99
30-day mortality 4 studies; N = 1089	199/620 (32.1)	193/469 (41.1)	OR 0.73 (0.46, 1.16)	*Favours intervention* *p* = 0.03 Substantial heterogeneity I^2 = 67%
Brinck 2016	35/206 (16.9)	39/146 (26.5)	OR 0.56 (0.34, 0.94)	*p* = 0.032
Cotton 2009	54/125 (43.2)	88/141 (62.4)	OR 0.46 (0.28,0.75)	*p* = 0.001
Dirks 2010	47/156 (30.1)	24/97 (24.7)	OR 1.31 (0.74, 2.33)	*p* = 0.382
Shaz 2010	63/132 (48)	42/84 (50)	OR 0.91 (0.53, 1.58)	*p* = 0.47
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. Majority of the included studies were conducted in civilian trauma patients which is applicable to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. Almost all studies were conducted in civilian trauma patients, of which most were in the US. Findings could be appropriately translated to the Australian healthcare context.				
Additional comments				
Authors conclusions: The implementation of a MTP is shown to provide a statistically and clinically significant reduction in the overall mortality of trauma patients. It is recommended that all centres providing care to severely injured bleeding patients have a MTP in place. *Included studies:* Brinck 2016, Cotton 2009, Dirks 2010, Hwang 2018, Maciel 2015, Noorman 2016, Nunn 2017, O'Keeffe 2008, Riskin 2009, Shaz 2010, Simmons 2010, Sinha 2013, Sisak 2012, van der Meij 2019				

CI, confidence interval; MA, meta-analysis MTP, massive transfusion protocol; NR, not reported; OR, odds ratio; SR, systematic review; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Kinslow 2020
Citation
Kinslow K, McKenney M, Boneva D, Elkbuli A. Massive transfusion protocols in paediatric trauma population: a systematic review. Transfusion Medicine. 2020; 30: 333-342.
Affiliation/Source of funds
Details on funding are not provided. The authors declared no conflicts of interest. *Author affiliations:* All authors affiliated with the Department of Surgery, Kendall Regional Medical Center, Miami, Florida. MM and DB affiliated with the University of South Florida, Tampa, Florida.

STUDY DETAILS: Kinslow 2020			
Study design	**Level of evidence**	**Location**	**Setting**
SR of observational studies (33)	I-III	US	Paediatric trauma
Intervention		**Comparator**	
MTP (activation criteria for all studies, physician discretion)		No MTP	
Population characteristics			
Paediatric trauma patients with various injury severity scores. One study (Edwards 2015) in combat population with predominately penetrative trauma. All other studies had majority blunt trauma.			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, Google Scholar, Cochrane Library, Embase, Wiley Online Library and OVID. No restrictions on date of publication were included. Authors do not provide details of search dates (e.g. inception to 1 January 2019)		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* No risk of bias for included studies was performed. Authors acknowledge limitations of individual studies, primarily differences in definitions in massive transfusion in paediatric patients.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (p-value)**
MTP versus No MTP				
Mortality 3 studies, N = 328 Chidester 2012 Hendrickson 2012 Hwu 2016	43/103 (41.7) 15/33 (45) 20/53 (38) 8/17 (47.1)	35/97 (36.1) 10/22 (45) 11/49 (23) 14/26 (53.8)	OR 1.31 (0.71, 2.42)[b] 1.00 (0.34, 2.95)[b] 2.09 (0.88, 5.00)[b] 0.76 (0.22, 5.29)[b]	p = 0.38 [b] I^2 = 5% (p = 0.35)[b] No significant difference No significant difference No significant difference
Thromboembolic events 1 study, N = 55 Chidester 2012	NR	NR	NR	NR Higher rates in the no-MTP group compared to the MTP group
Time to first transfusion 3 studies, N = 328 Chidester 2012 Hendrickson 2012 Hwu 2016	NR	NR	NR	NR Significant decrease in time to first transfusion observed in the MTP group compared to no MTP
Ventilator days 2 studies, N = 273 Hendrickson 2012 Hwu 2016	NR	NR	NR	NR No significant difference No significant difference
ICU Days 2 studies, N = 273 Hendrickson 2012	NR	NR	NR	NR No significant difference

STUDY DETAILS: Kinslow 2020				
Hwu 2016				No significant difference
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. Authors do not provide sufficient details regarding individual study findings making it difficult to confidently apply to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context. Authors do not provide details of study locations or sufficient details regarding individual study findings making it difficult to confidently apply to the Australian healthcare context.				
Additional comments				
Identifies same studies as Kamyszek 2019. *Authors conclusions:* Existing evidence trends in the direction of supporting balanced approaches in paediatric populations. This review is a narrative review only with a lack of individual study data limiting the ability to make sound conclusions. *Included studies:* Chidester 2012, Hendrickson 2012, Hwu 2016				

CI, confidence interval; ICU, intensive care unit; MTP, massive transfusion protocol; NR, not reported; SD, standard deviation; SR, systematic review; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Calculated post-hoc using RevMan 5.3

STUDY DETAILS: Kamyszek 2019			
Citation			
Kamyszek RW, Leraas HJ, Reed C, Ray CM, Nag UP, Poisson JL, Tracy ET. Massive transfusion in the pediatric population: A systematic review and summary of best-evidence practice strategies. J Trauma Acute Care Surg. 2019 Apr;86(4):744-754. doi: 10.1097/TA.0000000000002188. PMID: 30629007.			
Affiliation/Source of funds			
The authors declare no conflict of interest and no funding for the systematic review. All authors are affiliated with Duke University in Durham, North Carolina.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of cohort studies and case series	I-IV/V	Not specified	Paediatric, Level I/II trauma centres
Intervention		**Comparator**	
Post MHP (referred to as MTP)		Pre MHP implementation	
Population characteristics			
Paediatric patients receiving MT. Included studies used 7 unique definitions of MT. Studies before 2015 used ≥one total blood volume (TBV) transfused within 24 hours, while studies since 2015 use the definition of >40 mL/kg total blood product within 24 hours. *Studies with pre MTP vs post MTP outcomes:* Hwu 2016 – retrospective review in single institution ACS Level I paediatric trauma centre, N = 43/235 receiving MT, patients <18 years, mean age 9 years Chidester 2012 – prospective cohort study in single-institution Level I paediatric trauma centre, N = 22/55 receiving MT, patients aged 0 to 28 years with mean of 9.6 years Hendrickson 2012 – retrospective review in single-institution Level II paediatric trauma centre, N = 53/102 receiving MT, patients aged <18 years with mean of 6.2 years			
Length of follow-up		**Outcomes measured**	
Database searched: PubMed, EMBASE, Web of Science Search dates: January 1946 to December 2017		In-hospital Mortality ICU Total length of stay	

Articles restricted to human subjects and written in English language only	Ventilator use Time to administration of first blood product (RBC, FFP, PLT)

INTERNAL VALIDITY

Overall QUALITY of the systematic review (descriptive)

Rating (AMSTAR): Critically low

Description: More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies.

Risk of bias of included studies: The review did not restrict included studies by Study design and thus included heterogenous group of studies. These included case reports and surveys. The review authors did not conduct an assessment of the risk of bias for the included studies.

RESULTS:

Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Post MHP vs Pre MHP				
Mortality (In hospital) 3 studies (N = 200) Hwu 2016 Chidester 2012 Hendrickson 2012	 8/17 (47.1%) 15/33 (45%) 20/53 (38%)	 14/26 (53.8%) 10/22 (45%) 11/49 (23%)	 NR NR NR	No significant difference *p* = 0.729 *p* > 0.05 *p* = 0.10
Mortality (24-hour) 1 study (N = 43) Hwu 2016	 6/17 (35.3%)	 10/26 (38.5%)	 NR	No significant difference *p* = 0.994
Total LOS (days, mean) 1 study (N = 21) Hwu 2016	 N = 17 45.8 ± 30.9	 N = 26 39.0 ± 30.1	 NR	No significant difference *p* = 0.619
ICU LOS (days, mean) 1 study (N = 43) Hwu 2016	6.0 ± 7.6 N = 17	4.3 ± 5.8 N = 26	NR	No significant difference *p* = 0.330
ICU LOS (days, median) 1 study (N = 102) Hendrickson 2012	7.0 N = 53	9.0 N = 49	NR	No significant difference *p* = 0.54
Ventilator use (days) 2 studies (N = 145) Hwu 2016 Hendrickson 2012	 8.3 (N = 17) 2.0 free days (N = 53)	 7.0 (N = 26) 6.0 free days (N = 49)	 NR NR	No significant difference *p* = 0.584 *p* = 0.27
Bleeding/thrombosis 1 study (N = 55) Chidester 2012	0% N = 22	12% N = 33	NR	*Favours intervention* *p* = 0.04
Hours to first blood product 1 study (N = 43) Hwu 2016	(mean) 0.9 (n = 17)	(mean) 0.8 (n = 26)	NR	No significant difference *p* = 0.688
Hours to first RBC 1 study (N = 43) Hwu 2016	(mean) 1.4 (n = 17)	(mean) 0.8 (n = 26)	NR	No significant difference *p* = 0.180
Hours to first FFP 2 studies (N = 102) Hwu 2016 Hendrickson 2012	(mean) 1.0 (n = 17) 0.8 (n = 53)	(mean) 2.7(n = 26) 3.3 (n = 49)	 NR NR	*Favours intervention* *p* = 0.005 *p* < 0.001

Hours to first PLT 1 study (N = 43) Hwu 2016	(mean) 4.4 (n = 17)	(mean) 6.0 (n = 26)	NR	No significant difference *p* = 0.421
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population but could be sensibly applied. Includes studies with various definition of paediatric MT.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The SR does not provide the location for the included studies, however the included studies with relevant outcomes were conducted in single institution Level I or II paediatric trauma centres.				
Additional comments				
Authors conclusions: A heterogeneous composite of 29 articles was included in the analysis. Current practices of paediatric MT demonstrate a variety of site-specific interventions with a persistently high mortality rate. Unfortunately, in aggregating these studies, the authors found that implementation of an MTP did not significantly reduce mortality or major morbidity. This paradox may be explained by the lack of adherence to protocol guidelines for blood product ratios in the paediatric studies reviewed, which could have mitigated expected mortality benefits. *Included studies:* Hwu 2016, Hendrickson 2012, Chidester 2012				

CI, confidence interval; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; LOS, length of stay; MD, mean difference; MT, massive transfusion; MTP, massive transfusion protocol; PLT, platelets; PP, per-protocol; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

Randomised controlled trials

No additional studies identified.

Observational / cohort studies

No additional studies identified.

E3 RBC ratios, timing, dose (Question 3)

Systematic reviews/meta-analyses

STUDY DETAILS: Tapia 2013			
Citation			
Tapia, N. M., Suliburk, J., & Mattox, K. L. (2013). The initial trauma center fluid management of penetrating injury: a systematic review. Clinical orthopaedics and related research, 471(12), 3961–3973. doi:10.1007/s11999-013-3122-4			
Affiliation/Source of funds			
Source of Funding: Details on funding not provided. *Author affiliations:* Baylor College of Medicine, Houston, USA *Conflict of interest*: The authors declared no conflicts of interest including possible conflicts of interest due to funding.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of 20 observational studies (including 15 retrospective comparative studies)	I-III	North America, Europe and Australia	Military and civilian studies with trauma patients
Intervention		**Comparator**	
Balanced ratios of blood transfusion according to damage control resuscitation principles		Alternate blood volume resuscitation strategy	
Population characteristics			
Trauma patients with at least 30% penetrating injury who receive massive transfusion			
Length of follow-up		**Outcomes measured**	
Databases: PubMed, Cochrane Library and Current Controlled Trials Register Citations published in the last 10 years prior to 2013		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The review does not comment on the risk of bias of included studies. Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies and only the studies scoring 6 or more were included in the review. However, no further detail about the NOS or its scoring system was provided.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
High vs low FFP:RBC or Plt:RBC ratios				
Mortality (30 days) 20 studies	NR	NR	NR	No meta-analysis performed Higher ratios associated with improved mortality in all trauma patients
14 studies	NR	NR	NR	
6 studies	NR	NR	NR	No significant difference after implementation of MTP with higher ratios or comparing ratios retrospectively in all trauma patients
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. 12/20 studies had more blunt than penetrating injuries. The review also included five combat studies (Borgman 2007, Cap 2012, Duchesne 2008, Pidcoke 2012 and Simmons 2011).				

STUDY DETAILS: Tapia 2013
Applicability (relevance of the evidence to the Australian health care system)
The evidence is directly applicable to the Australian healthcare context with few caveats. Three different definitions of massive transfusion were used in the included studies.
Additional comments
Authors conclusions: Patients with penetrating injuries who require massive transfusion should be transfused early using balanced ratios of RBC, FFP and platelets. *Included studies:* Pidcoke 2012, Holcomb 2012, Cap 2012, Sharpe 2012, Brown 2011, Rowell 2011, Sambasivan 2011, Simmons 2011, deBiasi 2011, Inaba 2011, Duchesne 2010, Inaba 2010, Shaz 2010, Dente 2009, Zink 2009, Holcomb 2008, Gunter 2008, Duchesne 2008, Cotton 2008, Borgman 2007

CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; MD, mean difference; NR, not reported; PLT, platelet; PP, per-protocol; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review; USA, United States America

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Jones 2016			
Citation			
Jones, AR and Frazier, SK. "Association of Blood Component Ratio With Clinical Outcomes in Patients After Trauma and Massive Transfusion: A Systematic Review." Advanced Emergency Nurse Journal. 2016; 38(2): 157-168.			
Affiliation/Source of funds			
Source of Funding: Details on funding not reported. *Author affiliations:* Dr Jones affiliated with Department of Acute, Chronic and Continuing Care, School of Nursing University of Alabama at Birmingham and Dr Frazier affiliated with College of Nursing, University of Kentucky, Lexington. *Conflict of interest*: The authors declared no conflicts of interest (p157)			
Study design	**Level of evidence**	**Location**	**Setting**
SR of 21 observational studies	I-III	Iraq (3), US (13), Germany (2), Australia (1), Japan (1), unknown (1)	Civilian Level I or major trauma centres (12) or military hospitals (4)
Intervention		**Comparator**	
Ratios (and supporting justifications) varied between studies with categorisations including high, medium or low, numerical ranges or a combination of both. High ratio of blood components (closest to 1:1 however, definitions varied across included studies up to 1:12)		Low ratio of blood components (from 1:20 to 1:1.5 in the included studies)	
Population characteristics			
Adult trauma patients, a mixture of blunt and penetrating trauma, who received massive transfusion as defined by the study's investigator Military population with penetrating injuries – Borgman 2007; Cap 2012; Perkins 2009 Patients with blunt trauma only – Brown 2012; Sperry 2008 Adult trauma patients – Duchesne 2008; Duchesne 2011; Holcomb 2008; Holcomb 2011; Gunter 2008; Inaba 2010; Kashuk 2008; Kudo 2014; Maegele 2008; Magnotti 201; Mitra 2010; Peiniger 2011; Snyder 2009; Teixeira 2009; Van 2010; Zink 2009			
Length of follow-up		**Outcomes measured**	
Databases: PubMed, CINAHL and MEDLINE (Ovid) **Citations published in English between 2007 and 2015**		Mortality (24 hours or 30 days) MOF Nosocomial infections ARDS ARF Sepsis LOS (hospital and ICU) or free days	

STUDY DETAILS: Jones 2016				
	Ventilator days or free days			
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The authors concluded the risk of bias for the included studies was low, although only two studies were prospective. Military studies were concluded to have a higher risk of bias. The most common sources of potential bias were lack of primary outcome reporting for mortality and LOS and AEs such as sepsis and ARDS. Mentions seven studies accounted for survival bias, a concept that certain patients may have been more likely to die earlier than others because they did not live long enough to receive the treatments necessary for survival.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
High vs low FFP:PRBC ratios				
Mortality (24 hours or 30 days) 17 studies	Meta-analysis not conducted: Administration of blood components close to or equalling 1:1:1 for RBCs:FFP:PLTs was significantly associated with reduced mortality in the majority of studies.			
10 studies Borgman 2007 Brown 2012 Duchesne 2008 Duchesne 2009 Gunter 2008 Holcomb 2008 Maegele 2008 Peiniger 2011 Teixeira 2009 Zink 2009	Significant survival benefit when the FFP:PRBC ratio approached 1:1 (decrease in mortality ranged from 4% to 64%)			
7 studies Kashuk 2008 Kudo 2014 Magnotti 2011 Mitra 2010 Snyder 2009 Sperry 2008 Van 2010	No difference in mortality based on FFP:PRBC ratio groups.			
Hospital LOS 4 studies Brown 2012 Maegele 2008 Peiniger 2011 Sperry 2008	Significant differences in hospital LOS between FFP:PRBC ratio groups – those who received high ratios experienced an average LOS of 15.5 days longer than those in the low ratio groups			
High vs low PLT:PRBC ratios				
Mortality (24 hours or 30 days)	Administration of blood components close to or equalling 1:1:1 for RBCs:FFP:PLTs was significantly associated with reduced mortality in the majority of studies			

STUDY DETAILS: Jones 2016				
7 studies Brown 2012 Gunter 2008 Holcomb 2008 Holcomb 2011 Inaba 2010 Perkins 2009 Zink 2009	Superior survival for both military and civilian patients who received a PLT:PRBC ratio closest to 1:1			
High vs low FFP:PRBC or PLT:PRBC ratios				
MOF 3 studies Cap 2012 Holcomb 2011 Maegele 2008	Significant difference in rates of MOF between high ratio (closer to 1:1) and low ratio groups Those in the low ratio groups experienced an average MOF rate of 27% compared with those in the high groups that experienced an average rate of 47%			
Hospital LOS/free days Holcomb 2008	6 ± 8 days	3 ± 7 days	NR	Favours combination of high ratios of both FFP:PRBCs and PLTs:PRBCs $p < 0.001$
ICU LOS/free days 4 studies Brown 2012 Maegele 2008 Mitra 2010 Peiniger 2011 3 studies Holcomb 2008 Holcomb 2011 Sperry 2008	 15.5 ± 4.4 days NR NR NR NR 7.5 ± 3.5 days NR NR NR	 14.1 ± 6.3 days NR NR NR NR 5.5 ± 3.5 days NR NR NR	 NR NR	 Subjects receiving ratios close to 1:1 required longer ICU LOS Subjects receiving ratios closer to 1:1 required shorter ICU LOS
Ventilation days 3 studies Maegele 2008 Mitra 2010 Sperry 2008	12 ± 3.6 days NR NR NR	7.8 ± 5.6 days NR NR NR	NR	Significant differences in duration between high and low ratios.
Ventilator-free days 4 studies Holcomb 2008 Holcomb 2011 Peiniger 2011 Zink 2009	9.5 ± 2.9 days NR NR NR NR	6 ± 2.9 days NR NR NR NR	NR	Subjects receiving higher ratio required shorter ventilation
Nosocomial infections 4 studies Borgman 2007 Kudo 2014 Perkins 2009 Snyder 2009	NR	NR	NR	No difference between ratio groups observed
ARDS 4 studies Borgman 2007	NR	NR	NR	No difference between ratio groups observed

STUDY DETAILS: Jones 2016				
Kudo 2014 Perkins 2009 Snyder 2009				
ARF 4 studies Borgman 2007 Kudo 2014 Perkins 2009 Snyder 2009	NR	NR	NR	No difference between ratio groups observed
Sepsis 4 studies Borgman 2007 Kudo 2014 Perkins 2009 Snyder 2009	NR	NR	NR	No difference between ratio groups observed
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. Three studies were conducted in Combat Support Hospitals in Iraq (Borgman 2007, Cap 2012 and Perkins 2009).				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context				
Additional comments				
Authors conclusions: Those who received high ratios experienced not only greater survival benefit but also higher rates of multiple-organ failure; all other clinical outcomes findings were equivocal. *Included studies:* Borgman 2007, Duchesne 2008, Gunter 2008, Holcomb 2008, Kashuk 2008, Maegele 2008, Sperry 2008, Duchesne 2009, Perkins 2009, Snyder 2009, Teixeira 2009, Zink 2009, Inaba 2010, Mitra 2010, Van 2010, Holcomb 2011, Magnotti 2011, Peiniger 2011, Brown 2012, Cap 2012, Kudo 2014				

AE, adverse events; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; CI, confidence interval; FFP: fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; LOS, length of stay; MD, mean difference; MOF, multi-organ failure; NR, not reported; PLT, platelet; PP, per-protocol; PRBC, packed red blood cell; RR, relative risk; SD, standard deviation; SR, systematic review; US; United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Poole 2016
Citation
Poole D, Cortegiani A, Chieregato A, Russo E, Pellegrini C, De Blasio E, Mengoli F, Volpi A, Grossi S, Gianesello L, Orzalesi V, Fossi F, Chiara O, Coniglio C, Gordini G; Trauma Update Working Group (2016). Blood Component Therapy and Coagulopathy in Trauma: A Systematic Review of the Literature from the Trauma Update Group. PloS one, 11(10), e0164090. doi:10.1371/journal.pone.0164090
Affiliation/Source of funds
Source of Funding: The authors received no specific funding for this work. *Author affiliations:* Anesthesia and Intensive Care Operative Unit, Belluno, Italy; Department of Biopathology and Medical Biotechnologies (DIBIMED), Section of Anesthesia, Analgesia, Intensive Care, and Emergency, University of Palermo, Italy; Neurointensive Care Unit ASST Great Metropolitan Hospital, Milan, Italy; Anaesthesia and Intensive Care Unit, Surgical and Severe Trauma Department, Hospital, Cesena, Italy; Anesthesia and Intensive Care, AO "Rummo", Benevento, Italy; UOC Intensive Care and Territorial Emergency Department, "Maggiore" Hospital, Bologna, Italy; Anesthesia and Intensive Care, AOU of Parma, Parma, Italy; Departmental Structure of Anesthesia and Intensive Care for Orthopedic Surgery, AOU "Careggi", Florence, Italy; Neuroanesthesia and Neurointensive Care, AOU "Careggi", CTO, Florence, Italy; Trauma Center Department, ASST Great Metropolitan Niguarda Hospital, Milan, Italy *Conflict of interest*: The authors declared no conflicts of interest.

STUDY DETAILS: Poole 2016			
Study design	**Level of evidence**	**Location**	**Setting**
SR of 9 observational studies + 1 RCT (Holcomb 2015) published after the conclusion of the literature search	I-III	NR US (Holcomb 2015)	Trauma
Intervention		**Comparator**	
Observational studies heterogenous, comparing several ratios. Individual study ratios not clearly reported Holcomb 2013: FFP/PRBC <1:2 Holcomb 2015: FFP/platelet/PRBA ratio 1:1:1		Observational studies heterogenous, comparing several ratios. Individual study ratios not clearly reported Holcomb 2013: FFP/PRBC ≥1:2 - <1:1 and ≥1:1 Holcomb 2015: FFP/platelet/PRBC ratio 1:1:2	
Population characteristics			
Adult trauma patients requiring transfusion			
Length of follow-up		**Outcomes measured**	
A literature search was conducted on Medline via PubMed (from inception- 14 December 2014).		Mortality (24-hours or 30-day)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and ***may not*** provide an accurate and comprehensive summary of the available studies that address the question of interest. *Risk of bias of included studies:* Not reported			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**1:1:1 ratio** **n/N (%)** **Mean ± SD**	**1:1:2 ratio** **n/N (%)** **Mean ± SD**	**Relative risk (95% CI)** **Hazard ratio (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
FFP/platelet/PRBC ratio 1:1:1 vs FFP/platelet/PRBC ratio 1:1:2				
Mortality, 24-hours N = 1552 (2 studies) Holcomb 2013 (N = 876)	FFP:PRBC ratio ≥1:1 FFP:PRBC ratio: ≥1:2 to <1:1 FFP:PRBC ratio <1:2 (ref) FFP:PRBC (Cont. Var.)		HR 0.23 (NA) HR 0.42 (NA) HR 1.00 (NA) HR 0.31 (0.16 ± 0.58)	No protective effect of high FFP/PRBC ratios between 6 and 24 hours or between 24 hours and 30 days
Holcomb 2015 (N = 676)	43/335 (12.8)	58/341 (17.0)	RR 0.75 (0.52, 1.09)	No significant difference NR
Mortality, 30-days N = 1552 (2 studies) Holcomb 2013 (N = 876)	FFP:PRBC ratio ≥1:1 FFP:PRBC ratio: ≥1:2-<1:1 FFP:PRBC ratio <1:2 (ref) FFP:PRBC (Cont. Var.)		HR 0.23 (NA) HR 0.42 (NA) HR 1.00 (NA) HR 0.31 (0.16±0.58)	No protective effect of high FFP/PRBC ratios between 6 and 24 hours or between 24 hours and 30 days
Holcomb 2015 (N = 676)	75/335 (22.4)	89/341 (26.1)	RR 0.86 (0.66, 1.12)	No significant difference *p* = NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The population from the included studies have not been described in detail.				

STUDY DETAILS: Poole 2016
Applicability (relevance of the evidence to the Australian health care system)
The evidence is directly applicable to the Australian healthcare context
Additional comments
Authors conclusions: Even if early (i.e. 6 hours from admission) protective effect of high ratios may be present (low evidence provided by observational study), in the medium and long period no beneficial effect is detected (high evidence from an RCT). High 1:1 FFP/PRBC ratios are not effective in determining a 12% mortality reduction compared to 1:2 ratios. The two studies were sufficiently homogeneous to provide cumulative "high" level evidence against the greater efficacy of 1:1 vs. 1:2 FFP/RPBC ratios *Included studies:* Holcomb 2013 (observational study), Holcomb 2015 (RCT included even though it was published after the literature search for this review was conducted)

CI, confidence interval; FFP, fresh frozen plasma; HR, higher ratio; ITT, intention-to-treat; MD, mean difference; NR, not reported; PP, per-protocol; PRBC, packed red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Cannon 2017			
Citation			
Cannon, J.W., Khan, M.A., Raja, A.S., Cohen, M.J., Como, J.J., Cotton, B.A., Dubose, J.J., Fox, E.E., Inaba, K., Rodriguez, C.J. and Holcomb, J.B., 2017. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. Journal of Trauma and Acute Care Surgery, 82(3), pp.605-617.			
Affiliation/Source of funds			
Source of Funding: Source of funding not disclosed *Author affiliations:* Author Bryan A. Cotton is a consultant, Haemonetics Corporation. *Conflict of interest*: The author declares no conflict of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of RCTs and cohort studies	I-III	NR	Trauma
Intervention		**Comparator**	
PICO 2: high ratio of plasma to RBC high ratio of platelet to RBC High ratio of plasma:RBC and platelet:RBC defined as close as possible to 1:1:1 (relatively more plasma and platelet).		**PICO 2:** low ratio of plasma to RBC low ratio of platelet to RBC Low ratio defined as less than or equal to 1:1:2 (relatively less plasma and platelet).	
Population characteristics			
Adult patients with severe trauma. *15 studies for Plasma:RBC ratios* (1 RCT: Holcomb 2015; 2 prospective observational studies: Kutcher 2014, Sperry 2008; 12 retrospective studies: Borgman 2007, Duchesne 2009, Guidry 2013, Halmin 2013, Holcomb 2008, Kim 2014, Magnotti 2011, Mitra 2010, Peiniger 2011, Shaz 2010, Snyder 2009, Teixeira 2009) *4 studies for Platelet:RBC ratios* (1 RCT: Holcomb 2015; 3 retrospective studies: Holcomb 2008, Perkins 2009, Shaz 2010)			
Length of follow-up		**Outcomes measured**	
Literature search of studies published in PubMed, MedLine and EMBASE from January 1985 to December 2015		Mortality (in hospital or 30 day) Blood products used (RBC in 24 hours)	

STUDY DETAILS: Cannon 2017				
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* **PICO 2:** Authors considered the overall quality of evidence to be moderate due to 1 RCT (high quality), 2 observational studies (moderate) balancing other low-quality retrospective studies. Heterogeneity was considered moderate for plasma:RBC data and high for platelet:RBC data.				
RESULTS:				
Outcome **No. trials (No. patients)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** ***p*-value (I^2)**
High vs low Plasma:RBC ratio				
Mortality, in hospital/ 30 day 14 studies (N = 5292) RCTs 1 study (N = 680) Holcomb 2015 Observational 2 studies (N = 558) Kutcher 2014 Sperry 2008 Retrospective 11 studies (N = 4054) Borgman 2007 Duchesne 2009 Halmin 2013 Holcomb 2008 Kim 2014 Magnotti 2011 Mitra 2010 Peiniger 2011 Shaz 2010 Snyder 2009 Teixeira 2009	**846/2771 (30.5)** 75/338 (22.2) **68/193 (35.2)** 39/91 (42.9) 29/102 (28.4) **703/2240 (31.4)** 31/162 (19.1) 13/46 (28.3) 69/335 (20.6) 87/252 (34.5) 22/66 (33.3) 25/66 (37.9) 44/167 (26.3) 317/871 (36.4) 41/100 (41) 24/60 (40 0 30/114 (26.3)	**968/2521 (38.4)** 89/342 (26.0) **139/365 (38.1)** 29/52 (55.8) 110/313 (35.1) **740/1814 (40.8)** 38/84 (45.2) 40/89 (44.9) 53/407 (13.0) 74/166 (44.6) 14/32 (43.8) 22/37 (59.5) 55/164 (33.5) 206/379 (54.4) 64/114 (56.1) 43/74 (58.1) 131/268 (48.9)	**OR 0.60 (0.46, 0.77)** OR 0.81 (0.57, 1.15) **OR 0.68 (0.46, 1.02)** OR 0.59 (0.30,1.18) OR 0.73 (0.45,1.20) **OR 0.56 (0.41, 0.77)** OR 0.29 (0.16,0.51) OR 0.48 (0.22,1.04) OR 1.73 (1.17,2.56) OR 0.66 (0.44,0.98) OR 0.64 (0.27,1.53) OR 0.42 (0.18,0.95) OR 0.71 (0.44,1.14) OR 0.48 (0.38,0.61) OR 0.54 (0.32,0.94) OR 0.48 (0.24,0.96) OR 0.37 (0.23,0.60)	*Favours intervention* $p < 0.0001$ Substantial heterogeneity $p < 0.00001$ ($I^2 = 72\%$) No significant difference $p = 0.24$ No significant difference $p = 0.06$ No significant heterogeneity $p = 0.63$ ($I^2 = 0\%$) *Favours intervention* $p = 0.0004$ Substantial heterogeneity $p < 0.00001$ ($I^2 = 77\%$)
Blood products used or RBC in 24 hours, units 5 studies (N = 1610) RCT 1 study (N = 679) Holcomb 2015 Observational 2 studies (N = 558)	**(n = 791)** 9 ± 7.4 (n = 338) **(n = 193)** 7 ± 1.7 (n = 91)	**(n = 819)** 9 ± 7.4 (n = 341) **(n = 375)** 10 ± 3.75 (n = 52)	**MD –1.42 (–4.39, 1.54)** MD 0.00 (–1.11, 1.11) **MD –4.26 (–7.17, 1.36)** MD –3.0 (–4.08, –1.92)	No significant difference $p = 0.35$ Substantial heterogeneity $p < 0.00001$ ($I^2 = 91\%$) No significant difference $p = 1.00$ *Favours intervention* $p = 0.004$ Substantial heterogeneity

STUDY DETAILS: Cannon 2017				
Kutcher 2014 Sperry 2008	16 ± 9 (n = 102)	22 ± 17 (n = 313)	MD -6.00 (–8.57, –3.43)	p = 0.03 (I^2 = 78%)
Retrospective 2 studies (N = 373)	**(n = 260)**	**(n = 113)**	**MD 0.84 (–9 .28, 10.95)**	No significant difference p = 0.87
Guidry 2013	19.3 ± 14.8 (n = 194)	13.9 ± 11 (n = 81)	MD 5.40 (2.23, 8.57)	Substantial heterogeneity
Kim 2014	26 ± 19.8 (n = 66)	31 ± 17.8 (n = 32)	MD –5.00 (–12.80, 2.80)	p = 0.02 (I^2 = 83%)
High vs low ratio Platelet:RBC				
Mortality, in hospital/ 30-days 4 studies (N = 1607)	**238/843 (28.2)**	**328/764 (42.9)**	**OR 0.44 (0.28, 0.71)** 181 fewer per 1000 (from 81 to 255 fewer)	*Favours intervention* p = 0.0006 Substantial heterogeneity p = 0.004 (I^2 = 78%)
RCTs 1 study (N = 680) Holcomb 2015	75/338 (22.2)	89/342 (26.0)	OR 0.81 (0.57, 1.15)	No significant difference p = 0.24
Retrospective 3 studies (N = 927)	**163/505 (32.3)**	**239/422 (56.6)**	**OR 0.36 (0.27, 0.47)** OR 0.38 (0.26,0.58)	*Favours intervention*
Holcomb 2008	67/234 (28.6)	94/184 (51.1)	OR 0.38 (0.24,0.61)	p < 0.00001
Perkins 2009	49/145 (33.8)	86/150 (57.3)	OR 0.29 (0.16,0.52)	No significant heterogeneity
Shaz 2010	47/126 (37.3)	59/88 (67.0)		p = 0.72 (I^2 = 0%)
Blood products used or RBC in 24 hours, units 1 RCT (N = 679) Holcomb 2015	9 ± 7.4 (n = 338)	9 ± 7.4 (n = 341)	MD 0.00 (–1.11, 1.11)	No significant difference p = 1.00
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
Overall, study population is generalisable to the guidelines population.				
Applicability (relevance of the evidence to the Australian health care system)				
Study is applicable to the Australian health care system.				
Additional comments				
Authors conclusions: The authors recommend targeting a high ratio of both plasma and platelet:RBC for resuscitating severely injured bleeding trauma patients. *List of relevant included studies:* Holcomb 2015, Kutcher 2014, Sperry 2008, Borgman 2007, Duchesne 2009, Guidry 2013, Halmin 2013, Holcomb 2008, Kim 2014, Magnotti 2011, Mitra 2010, Peiniger 2011, Shaz 2010, Snyder 2009, Teixeira 2009, Perkins 2009				

AR, absolute risk; CI, confidence interval; DCR; damage control resuscitation; ITT, intention-to-treat; MD, mean difference; MHP; Major haemorrhage protocol; NR, not reported; OR, odds ratio; PICO, population intervention comparator outcome; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

STUDY DETAILS: Rahouma 2017
Citation
Rahouma M, Kamel M, Jodeh D, Kelley T, Ohmes LB, de Biasi AR, et al. Does a balanced transfusion ratio of plasma to packed red blood cells improve outcomes in both trauma and surgical patients? A meta-analysis of randomized controlled trials and observational studies. The American Journal of Surgery. 2017; https://doi.org/10.1016/j.amjsurg.2017.08.045
Affiliation/Source of funds
Source of Funding: The authors declared that they received no funding for this study (pg8)

STUDY DETAILS: Rahouma 2017			
Author affiliations: M.R., M.K., D.J., LB.O., AR. dB., AA.A., TS.G., C.L., LN.G. & M.G. affiliated with Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY, USA; TK affiliated with Department of Surgery, Dwight D Eisenhower Army Medical Center, Augusta, GA, USA; UB affiliated with Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, UK; PCL affiliated with Cardiothoracic Surgery, Northwell Health, Hofstra Northwell School of Medicine, New York, NY, USA *Conflict of interest*: The authors declared no conflicts of interest. (pg8)			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of 34 observational studies and 2 RCTs	I	USA (26), Germany (3), Australia (1), Korea (1), Switzerland (1), Canada (1), UK (1) & China (1)	Trauma (military and civilian), Medical
Intervention		**Comparator**	
Higher FFP:RBC ratio		Contemporaneous patient cohorts with lower FFP:RBC ratio	
Population characteristics			
Mean age: 37.1 years for trauma only patients vs 66.7 years for non-trauma patients. 63% of studies were blunt trauma			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, MEDLINE, EMBASE, Web of Science, Science Direct, Google Scholar **Citations published up to 10 January 2016**		Mortality ARDS ALI	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. *Risk of bias of included studies:* No formal risk of bias was performed by the authors. The authors acknowledge that most the studies were observational raising concerns regarding the quality of available evidence. Many studies were limited by survival bias and length of time bias. The authors tried to be comprehensive rather than attempting to control for the inherent bias present in the observational studies.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**Low ratio** **n/N (%)** **Mean ± SD**	**High ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Low (<1:1) vs high ≥1:1) ratios FFP:RBC				
Mortality (24 hrs) N = 5265 (7 studies)	**696/3518 (19.8)**	**215/1747 (12.3)**	**OR 2.05 (1.55, 2.71)**	Mortality is more likely in lower ratio group (comparator) *p* = 0.03
RCT				
Holcomb 2015	58/342 (17)	43/338 (12.7)	OR 1.40 (0.91, 2.15)	Significant heterogeneity I^2 = 57%
Observational				
Duchesene 2009	84/196 (42.9)	33/189 (17.5)	OR 3.55 (2.22, 5.67)	
Maegele 2008	158/484 (32.6)	32/229 (14)	OR 2.98 (1.96, 4.54)	
Sharpe 2012	31/66 (47)	20/69 (29)	OR 2.17 (1.07, 4.41)	
Spoerke 2011	222/1498 (14.8)	14/146 (9.6)	OR 1.64 (0.93, 2.90)	
Undurraga 2015	29/172 (16.9)	23/174 (13.2)	OR 1.33 (0.74, 2.41)	
Wafaisade 2011	114/760 (15)	50/602 (8.3)	OR 1.95 (1.37, 2.77)	
Mortality 30 days N = 5266 (7 studies)	**1074/3689 (29.1)**	**361/1577 (22.9)**	**OR 1.36 (1.09, 1.69)**	Mortality is more likely to occur in lower ratio group (comparator)

STUDY DETAILS: Rahouma 2017				
RCT				*p* = 0.09
Holcomb 2015	89/342 (26)	75/338 (22.2)	OR 1.23 (0.87, 1.75)	Moderate heterogeneity
Nascimento 2013	3/32 (9.4)	11/37 (29.7)	OR 0.24 (0.06, 0.97)	I^2 = 45%
Observational				
Maegele 2008	222/484 (45.9)	76/229 (33.2)	OR 1.71 (1.23, 2.37)	
Spoerke 2011	351/1498 (23.4)	32/146 (21.9)	OR 1.09 (0.72, 1.64)	
Undurraga 2015	43/172 (25)	36/174 (20.7)	OR 1.28 (0.77, 2.11)	
Wafaisade 2011	205/760 (27)	118/602 (19.6)	OR 1.52 (1.17, 1.96)	
Zink 2009	161/401 (40.1)	13/51 (25.5)	OR 1.96 (1.01, 3.80)	
Low (<1:1.5) vs high ≥1:1.5) ratios FFP:RBC				
Mortality 24 hrs N = 1877 (4 studies)	**225/1072 (21)**	**103/805 (12.8)**	**OR 3.97 (1.37, 11.49)**	No significant difference *p* <.00001
Observational				Significant heterogeneity
Hardin 2014	113/432 (26.2)	78/470 (16.6)	OR 1.78 (1.29, 2.46)	I^2 = 88%
Lustenberger 2011	31/52 (59.6)	18/177 (15.4)	OR 13.04 (6.23, 27.27)	
Mitra 2010	41/275 (14.9)	3/56 (5.4)	OR 3.10 (0.92, 10.38)	
Sperry 2008	40/313 (12.8)	4/102 (3.9)	OR 3.59 (1.25, 10.29)	
Mortality 30 days N = 453 (5 studies)	**268/981 (27.3)**	**185/832 (22.2)**	**OR 2.45 (1.14, 5.25)**	No significant difference *p* < 0.00001
Observational				Significant heterogeneity
Borgman 2007	38/84 (45.2)	31/162 (19.1)	OR 3.49 (1.95, 6.24)	I^2 = 87%
Brown 2012	68/476 (14.9)	8/116 (6.9)	OR 2.25 (1.05, 4.82)	
Lustenberger 2011	36/52 (69.2)	34/177 (19.2)	OR 9.46 (4.71, 19.01)	
Mitra 2010	16/56 (28.6)	83/275 (30.2)	OR 0.93 (0.49, 1.74)	
Sperry 2008	110/313 (35.1)	29/102 (28.4)	OR 1.36 (0.84, 2.22)	
Low (<1:2) vs high (≥1:2) ratios FFP:RBC				
Mortality (24 hrs) N = 3540 (9 studies)	**535/1370 (39.1)**	**398/2170 (18.3)**	**OR 2.85 (2.14, 3.81)**	Mortality is more likely to occur in lower ratio group (comparator) *p* = 0.01
Observational				Significant heterogeneity
Borgman 2011	83/237 (35)	86/422 (20.4)	OR 2.11 (1.47, 3.01)	I^2 = 59%
Dente 2009	7/23 (30.4)	7/50 (14)	OR 2.69 (0.81, 8.87)	
Kashuk 2008	44/81 (54.3)	23/59 (39)	OR 1.86 (0.94, 3.68)	
Kim 2014	9/32 (28.1)	2/68 (2.9)	OR 12.91 (2.60, 64.21)	
Magnotti 2011	13/37 (35.1)	7/66 (10.6)	OR 4.57 (1.62, 12.84)	
Peiniger 2011	159/379 (42)	157/871 (18)	OR 3.29 (2.52, 4.29)	
Rowell 2011	128/375 (34.1)	71/328 (21.6)	OR 1.88 (1.34, 2.63)	
Shaz 2010	66/114 (57.9)	20/100 (20)	OR 5.50 (2.97, 10.17)	
Stanworth 2015	26/92 (28.3)	25/206 (12.1)	OR 2.85 (1.54, 5.29)	
Mortality (30 days) N = 1904 (14 studies)	**978/2695 (36.3)**	**926/3498 (26.5**)	**OR 1.77 (1.50, 2.10**)	Mortality is more likely to occur in lower ratio group (comparator) *p* = 0.08
RCT				Moderate heterogeneity
Holcomb 2008	128/214 (59.8)	103/256 (40.2)	OR 2.21 (1.53, 3.20)	I^2 = 37%
Observational				
Borgman 2011	113/237 (47.7)	147/422 (34.8)	OR 1.70 (1.23, 2.36)	
Brown 2011	35/186 (18.8)	25/215 (11.6)	OR 1.76 (1.01, 3.07)	

STUDY DETAILS: Rahouma 2017				
Duchesene 2009	30/63 (47.6)	23/72 (31.9)	OR 1.94 (0.96, 3.90)	
Kim 2014	14/32 (43.8)	22/68 (32.4)	OR 1.63 (0.69, 3.86)	
Mazzeffi 2016	13/88 (14.8)	28/364 (7.7)	OR 2.08 (1.03, 4.20)	
Mell 2010	16/41 (39)	13/87 (14.9)	OR 3.64 (1.54, 8.62)	
Peiniger 2011	203/379 (53.6)	317/871 (36.4)	OR 2.08 (1.63, 2.66)	
Rowell 2011	167/375 (44.5)	113/328 (34.5)	OR 1.53 (1.13, 2.07)	
Shaz 2010	50/114 (43.9)	41/100 (41)	OR 1.12 (0.65, 1.94)	
Snyder 2008	43/74 (58.1)	28/60 (46.7)	OR 1.59 (0.80, 3.15)	
Spinella 2011	22/185 (11.9)	25/276 (9.1)	OR 1.36 (0.74, 2.48)	
Teixeira 2009	131/268 (48.9)	30/115 (26.1)	OR 2.71 (1.68, 4.38)	
Van 2010	10/439 (2.3)	11/264 (4.2)	OR 0.54 (0.22, 1.28)	
FFP:RBC ratios (general)				
ARDS (8 studies) RCT Holcomb 2015 Observational Brown 2012 Kim 2014 Lustenberger 2011 Nascimento 2013 Sperry 2008 Undurraga 2016 Van 2010	NR	NR	OR 0.68 (0.40,1.16)	There was no difference in the incidence of ARDS with respect to FFP: RBC ratio *p* = 0.16
ALI (2 studies) RCT Holcomb 2015 Observational Kim 2014	NR	NR	OR 1.23 (0.81,1.86)	There were no differences observed in the incidence of ALI *p* = 0.34
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats				
Additional comments				
Authors conclusions: Our data suggests that there is a survival benefit at 24 h and 30 days when this practice is followed, with the largest benefit within 24 h. A ratio of 1:1.5 was associated with the highest survival benefit. *List of relevant included studies* Borgman 2007, Borgman 2011, Brown 2011, Brown 2012, De Biasi 2011, Dente 2009, Duchesne 2008, Duchesne 2009, Gunter 2008, Hardin 2014, Holcomb 2015, Holcomb 2008, Kashuk 2008, Kim 2014, Lustenberger 2011, Maegele 2008, Magnotti 2011, Mazzeffi 2016, Mell 2010, Peiniger 2011, Rowell 2011, Sharpe 2012, Shaz 2010, Synder 2008, Sperry 2008, Spinella 2011, Stanworth 2015, Teixeira 2009, Undurraga Peri 2015,Van 2010, Wafaisade 2011, Yang 2015, Zink 2009				

ARDS, acute respiratory distress syndrome; ALI, acute lung injury; CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; MD, mean difference; NR, not reported; OR, odds ratio; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; UK, United Kingdom; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Maw 2018			
Citation			
Maw 2018 Maw G. & Furyk C. Pediatric Massive Transfusion. A Systematic Review. Pediatric Emergency Care. 2018; 34 (8), pp.594-598.			
Affiliation/Source of funds			
Source of *Funding:* None reported *Author affiliations:* GM affiliated with Australasian College for Emergency Medicine; and CF affiliated with Australian and New Zealand College of Anaesthetists, Melbourne, Australia. *Conflict of interest*: Authors declare no conflict of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of 4 nonrandomised trials (3 retrospective analyses and one non-randomised prospective study)	I-III	Hendrickson 2012 – US Chidester 2012 – US Edwards 2015 – Iraq and Afghanistan Nosanov 2013 - US	Trauma (level I & II centres, military hospitals)
Intervention		**Comparator**	
Hendrickson 2012 – MTP: designed for 5 different weight ranges (each pack containing equal volumes of PRBCs and FFP) Chidester 2012 – uncrossmatched blood via MTP Edwards 2015 – higher doses of FFP/PRBCs and high volume of crystalloid Nosanov 2013 – high ratios of plasma/platelets to PRBCs		Hendrickson 2012 – Pre MTP: blood products at physician discretion (not described) Chidester 2012 – uncrossmatched blood at physician discretion Edwards 2015 – comparison at varying doses Nosanov 2013 – low, medium of plasma/platelets to PRBCs	
Population characteristics			
Paediatric patients, younger than 18 years, with traumatic injury requiring blood transfusion			
Length of follow-up		**Outcomes measured**	
Databases searched: CENTRAL, MEDLINE, EMBASE, Web of Science, The Joanna Briggs Institute EBP Database, CINAHL and AUSTHealth. No date restriction with the search run on February 29, 2016.		30-day mortality Unnecessary transfusion (morbidity and waste) Avoidable complications including ICU days and ventilator days	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* All four included studies were of very low quality. This assessment was based mainly on high risk of selection bias and lack of allocation concealment.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
MTP versus No MTP				
Mortality				No significant difference
Hendrickson 2012 (N = 102)	20/53 (38%)	11/49 (23%)	NR	(implied a trend towards poorer outcomes with MTP use).[b]
Chidester 2012 (N = 55)	45%	45%	NR	No significant difference. [c]
Ventilator days				

STUDY DETAILS: Maw 2018				
Hendrickson 2012 (N = 102)	Median 2 days	Median 6 days	NR	NR
ICU days Hendrickson 2012 (N = 102)	Median 7 days	Median 9 days	NR	NR
Thromboembolic events Chidester 2012 (N = 55)	NR	NR	NR	MTP in this study associated with fewer thromboembolic events
Varying ratios of FFP/PRBCs				
Mortality Edwards 2015 (N = 301)	NR	NR	NR	Patients did not benefit from ratios approaching 1:1 and found non-significant trends towards increased mortality with higher FFP/PRBC ratios
Nosanov 2013 (N = 105)	NR	NR	NR	No difference between groups
High vs low volume of crystalloid (>150 mL/kg vs <150 mL/kg)				
Mortality Edwards 2015	18%	10%	NR	Favours comparator (*p* = NR) Crystalloid infusions of >150 mL/kg were associated with significantly higher mortality
ICU days Ventilator days Edwards 2015	NR	NR	NR	Favours comparator (*p* = NR) Crystalloid infusions of >150 mL/kg were associated with significantly higher ICU and ventilator days
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. Edwards 2015 was a retrospective review of 1300 injured children presenting to US military hospitals in Afghanistan and Iraq via a trauma database.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The reviewer's state there is variability in the definition of massive transfusion in children. Additionally, the definition of MTP used in the studies in not clear.				
Additional comments				
Authors conclusions: There is little evidence for improved outcomes using component-based transfusion in a rigid 1:1:1 strategy in children. A goal-directed approach using viscoelastic haemostatic assay–guided treatment with early institution of tranexamic acid and fibrinogen replacement is considered the way forward. This recommendation is based upon very low-quality evidence. *List of relevant included studies:* Hendrickson 2012, Chidester 2012, Edwards 2015, Nosanov 2013 21 further articles were deemed relevant but are not listed individually.				

CI, confidence interval; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; MD, mean difference; MTP, massive transfusion protocol; NR, not reported; PP, per-protocol; PRBC, packed red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Authors concluded that MTP resulted in increased ratio of FFP:PRBC but did not change in-hospital mortality.

c. Authors conclude that MTP had no effect on mortality (there was a trend towards poorer outcomes) compared with transfusion at physician discretion.

STUDY DETAILS: McQuilten 2018

Citation

McQuilten 2018

McQuilten ZK, Crighton G, Brunskill S, *et al*. Optimal dose, timing and ratio of blood products in massive transfusion: Results from a systematic review. *Transfusion Medicine Reviews*. 2018, 32: 6–15

Affiliation/Source of funds

Source of funds: Funding support from Australian National Blood Authority. McQuilten received funding support from National Health and Medical Research Council (NHMRC) Early Career Fellowship and NHMRC Centre for Research Excellence in Patient Blood Management in Critical Care and Trauma.

Conflicts of interest: Transfusion Research Unit of Monash University received financial support from Australian Red Cross Blood Service, New Zealand Blood Service, Victorian Department of Health and CSL Behring for the Australian and New Zealand Massive Transfusion Registry.

Author affiliations: Transfusion Research Unit, Monash University; Australian and New Zealand Intensive Care Research Centre; Systematic Reviews Initiative, NHS Blood and Transplant/Oxford University Hospitals NHS Trust

Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs	I	North America, US, UK	Trauma centre

Intervention	**Comparator**
Blood component therapy (FFP, platelets, CRYO or fibrinogen concentrate) to RBCs Holcomb 2015: 1:1:1 ratio 6 U FFP: 1 PLT (~pool of 6 U): 6 RBC Transfused PLT first then alternating RBC and plasma units Nascimento 2013: 1:1:1 ratio Fixed ratio of FFP:PLT:RBC	Dose, timing or ratio comparisons Holcomb 2015: 1:1:2 ratio First pack 3 U FFP; 0 PLT: 6 U RBC (transfused 2 U RBC alternating 1 U FFP) Alternate pack 3 U FFP: 1 PLT: 6 U RBC (transfused PLT first, 2 U RBC alternating with 1 U plasma) Nascimento 2013: Standard practice guided by laboratory tests. Participants achieved 1:0.8:2 ratio of FFP:PLT:RBC

Population characteristics

Paediatric and/or adult who had critical bleeding and had received, or was anticipated to receive, a massive transfusion and measured at least one outcome of interest

Length of follow-up	**Outcomes measured**
Databases: Embase, Medline, PubMed, CENTRAL, DARE and NHSEED (The Cochrane Library), Transfusion Evidence Library Search dates: inception to 21 February 2017	Mortality, morbidity, transfusion requirements

INTERNAL VALIDITY

Overall QUALITY of the systematic review (descriptive)

Rating (AMSTAR): High

Description: No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

Risk of bias of included studies: The main sources of bias risk were lack of blinding of participants and/or clinical and research staff and small sample sizes.

RESULTS:

Outcome **No. trials (No. patients)**	**Low ratio (1:1:1)** **n/N (%)** **Mean ± SD**	**High ratio (1:1:2)** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** ***p*-value (I^2)**
Transfusion ratio 1:1:1 versus Transfusion ratio 1:1:2 (Question 3)				
28-day mortality (N = 755)	88/378 (23.28)	94/377 (24.93)	RR 1.26 (0.49, 3.22)	No significant difference *p* = 0.64
Holcomb 2015	75/338 (22.2)	89/342 (26)	0.85 (0.65, 1.11)	Moderate heterogeneity
Nascimento 2013	13/40 (32.5)	5/35 (14.3)	2.27 (0.90, 5.74)	*p* = 0.05 (I^2 = 75%)

STUDY DETAILS: McQuilten 2018				
ARDS (N = 680) Holcomb 2015	46/338 (13.6)	48/342 (14)	RR 0.97 (0.67, 1.41)	*p* = NR
AKI (N = 680) Holcomb 2015	74/338 (21.9)	85/342 (24.9)	RR 0.88 (0.67, 1.16)	*p* = NR
Sepsis (N = 680) Holcomb 2015	99/338 (28.9)	91/342 (26.6)	RR 1.10 (0.86, 1.40)	*p* = NR
MOF (N = 680) Holcomb 2015	20/338 (5.9)	15/342 (4.4)	RR 1.35 (0.70, 2.59)	*p* = NR
MI (N = 680) Holcomb 2015	0/338 (0)	2/342 (0.6)	RR 0.20 (0.01, 4.20)	*p* = NR
Stroke (N = 680) Holcomb 2015	8/338 (2.4)	11/342 (3.2)	RR 0.74 (0.30, 1.81)	*p* = NR
DVT (N = 680) Holcomb 2015	25/338 (7.4)	24/342 (7.0)	RR 1.05 (0.61, 1.81)	*p* = NR
Pulmonary embolus (symptomatic) (N = 680) Holcomb 2015	14/338 (4.1)	13/342 (3.8)	RR 1.09 (0.52, 2.28)	*p* = NR
Hospital-free days (N = 755) Holcomb 2015 (N = 680) Nascimento 2013 (N = 75)	Median (IQR) 1 (0-17) 0 (0-15)	Median (IQR) 0 (0-16) 1.5 (0-12)	 Not estimable Not estimable	 No significant difference *p* = 0.83 No significant difference *p* = 0.39
ICU-free days (N = 755) Holcomb 2015 (N = 680) Nascimento 2013 (N = 75)	Median (IQR) 5 (0-11) 23 (12-26)	Median (IQR) 4 (0-10) 20 (5-24)	 Not estimable Not estimable	 No significant difference *p* = 0.10 No significant difference *p* = 0.27
RBC in 24 hours (N = 680) Holcomb 2015	Median (IQR) 9 (5-15)	Median (IQR) 9 (9-16)	Not estimable	No significant difference *p* = 0.30
FFP in 24 hours (N = 680) Holcomb 2015	Median (IQR) 7 (3-13)	Median (IQR) 5 (2-10)	Not estimable	*Favours intervention* *p* < 0.001
PLT in 24 hours (N = 680) Holcomb 2015	Median (IQR) 12 (6-18)	Median (IQR) 6 (0-12)	Not estimable	*Favours intervention* *p* < 0.001
CRYO in 24 hours (N = 680) Holcomb 2015	Median (IQR) 0 (0-0)	Median (IQR) 0 (0-9)	Not estimable	*Favours intervention* *p* = 0.01
Number receiving >0 units CRYO in 24 hours (N = 680)	73/338 (21.6)	100/342 (29.2)	RR 0.74 (0.57, 0.96)	*p* = NR

STUDY DETAILS: McQuilten 2018				
Holcomb 2015				
Total blood products transfused to 24 hours (N = 680) Holcomb 2015	Median 25.5	Median 19	Not estimable	*p* = NR
Transfusion ratio of 1:1:1 achieved (N = 75) Nascimento 2013	21/37 (57)	2/32 (6)	9.08 (2.31, 35.77)	*p* < 0.01
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The study population in the systematic review is consistent with the Guideline's target population, i.e. patients who had critical bleeding and had received (or was anticipated to receive) a massive transfusion.				
Applicability (relevance of the evidence to the Australian health care system)				
Holcomb (2015) was conducted in major trauma centres around North America. Nascimento (2013) and Nascimento (2016) were conducted in a single trauma centre in Canada. Curry (2015) was conducted in two major civilian trauma centres in the UK. Nascimento (2013), Nascimento (2016) and Curry (2015) were conducted in a health system similar to Australia.				
Additional comments				
Authors conclusion: Overall, there was no evidence of a difference in mortality between a 1:1:1 ration of FFP, PLT and RBC compared to 1:1:2 transfusion strategy or standard transfusion practice guided by laboratory parameters *List of included relevant studies* Holcomb 2015, Nascimento 2013, Nascimento 2016, Curry 2015				

AKI, Acute kidney injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; CRYO, cryoprecipitate; DVT, deep vein thrombosis; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IQR, inter quartile range; MD, mean difference; MOF, multiple organ failure; MI, myocardial infarction; PLT, platelet; PP, per-protocol; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: da Luz 2019			
Citation			
da Luz LT, Shah PS, Strauss R, Mohammed AA, D'Empaire PP, Tien H, et al. Does the evidence support the importance of high transfusion ratios of plasma and platelets to red blood cells in improving outcomes in severely injured patients: a systematic review and meta-analysis. Transfusion Medicine. 2019; 59: 3337-3349.			
Affiliation/Source of funds			
Author affiliations: LTdL, RS, AAM, HT, ABN and BN affiliated with Department Surgery, Sunnybrook Health Sciences Centre; PSS affiliated with Department of Pediatrics, Mount Sinai Hospital; and PPDE affiliated with Department Anesthesia, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada. Details on funding are not provided. The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of RCTs (2) and observational studies (53)	I-II/III	US, Japan, Multicentre, UK, Europe, Australia	Trauma (civilian and military), single and multi-centre settings
Intervention		**Comparator**	
High ratios of FFP and/or PLTs:RBC		Lower ratios of FFP and/or PLTs:RBC	
Population characteristics			
Adult trauma patients (≥15 years) NOTE: Glaser 2015, Hardin 2014 in combat/military population. Haltmeier 2017 in TBI population			
Length of follow-up		**Outcomes measured**	
Databases searched: Medline, Embase, Cochrane Controlled Trials Register from inception to 31 July 2018		Mortality, 24 hours	

STUDY DETAILS: da Luz 2019				
Also searched ClinicalTrials.gov and Google Scholar (first 200 hits)		Mortality, 30-days Allogenic blood products		
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* Overall, the evidence was of low quality for both mortality and exposure to allogenic blood products. The main limitation of the review is that most data are observational and thus survival bias, confounding, and publication bias are unavoidable.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
FFP:PLTS:RBCs high (1:1:1) versus low (approximately 1:1:2)				
Mortality, 28/30 days 2 RCTs, N = 749	88/378 (23.3)	94/377 (25)	OR 1.35 (0.40, 4.59)	*No significant difference* *p* = 0.63
Holcomb 2015	75/338 (22.2)	89/342 (26)	OR 0.81 (0.57, 1.15)	Substantial heterogeneity
Nascimento 2013	13/40 (32.5)	5/35 (14.3)	OR 2.89 (0.91, 9.17)	I^2 = 76% (*p* = 0.04)
FFP:RBC 1:1 versus <1:1				
Mortality, 24 hours 5 observation studies N = 2414	126/738 (17.1)	420/1676 (25.1)	OR 0.34 (0.14, 0.82)	*Favours high ratio* *p* = 0.02 Substantial heterogeneity
Balvers 2017	89/210 (42.4)	65/169 (38.5)	OR 1.18 (0.78, 1.78)	I^2 = 88% (*p* <0.00001)
Maegele 2008	13/115 (11.3)	158/484 (32.6)	OR 0.26 (0.14, 0.48)	
Perkins 2009	5/96 (5.2)	75/209 (35.9)	OR 0.10 (0.04, 0.25)	
Vulliamy 2017	8/107 (7.5)	9/54 (16.7)	OR 0.40 (0.15, 1.12)	
Wafaisade 2011	11/210 (5.2)	113/760 (14.9)	OR 0.32 (0.17, 0.60)	
Mortality, 30-days 10 observation studies N = 4203	308/1270 (24.3)	922/2933 (31.4)	OR 0.38 (0.22, 0.68)	*Favours high ratio* *p* = 0.001 Substantial heterogeneity
Duchesne 2008	18/71 (23.4)	56/64 (87.5)	OR 0.05 (0.02, 0.12)	I^2 = 91% (p <0.0001)
Duchesne 2009	13/46 (28.3)	22/43 (51.2)	OR 0.38 (0.16, 0.90)	
Haltmeier 2017	53/156 (34)	46/86 (53.5)	OR 0.45 (0.26, 0.77)	
Holcomb 2011	65/216 (30.1)	101/211 (47.9)	OR 0.47 (0.32, 0.70)	
Maegele 2008	28/115 (24.3)	220/484 (45.5)	OR 0.39 (0.24, 0.61)	
Perkins 2009	15/96 (15.6)	86/150 (57.3)	OR 0.14 (0.07, 0.26)	
Sambasivan 2011	47/202 (23.3)	126/979 (12.9)	OR 2.05 (1.41, 2.99)	
Vulliamy 2017	25/107 (23.4)	15/54 (27.8)	OR 0.79 (0.38, 1.67)	
Wafaisade 2011	31/210 (14.8)	194/760 (25.5)	OR 0.51 (0.33, 0.76)	
Zink 2009	13/51 (25.5)	56/102 (54.9)	OR 0.28 (0.13, 0.59)	
FFP:RBC 1:1.5 versus <1:1.5				
Mortality, 24 hours 2 observation studies N = 118	10/58 (17.2)	19/60 (31.7)	OR 0.43 (0.18, 1.06)	*Favours high ratio* *p* = 0.07 No heterogeneity
Bui 2016	7/49 (14.3)	17/54 (31.5)	OR 0.36 (0.14, 0.97)	I^2 = 0% (*p* = 0.41)

STUDY DETAILS: da Luz 2019				
Kudo 2013	3/9 (33.3)	2/6 (33.3)	OR 1.00 (0.11, 8.95)	
Mortality, 30-days 5 observation studies N = 1369	123/715 (17.2)	219/654 (33.5)	OR 0.42 (0.22, 0.81)	*Favours high ratio* *p* = 0.01 Substantial heterogeneity I^2 = 73% (*p* = 0.005)
Borgman 2007	31/162 (19.1)	20/31 (64.5)	OR 0.13 (0.06, 0.30)	
Hardin 2014	36/283 (12.7)	82/283 (29)	OR 0.36 (0.23, 0.55)	
Kudo 2013	4/9 (44.4)	2/6 (33.3)	OR 1.60 (0.19, 13.70)	
Lustenberger 2011	23/159 (14.5)	5/21 (23.8)	OR 0.54 (0.18, 1.62)	
Sperry 2008	29/102 (28.4)	110/313 (35.1)	OR 0.73 (0.45, 1.20)	
FFP:RBC 1:2 versus <1:2				
Mortality, 24 hours 6 observation studies N = 1388	134/664 (20.2)	226/724 (31.2)	OR 0.59 (0.43, 0.81)	*Favours high ratio* *p* = 0.001 Mild heterogeneity I^2 = 22% (*p* = 0.27)
Holcomb 2008	33/83 (40)	64/151 (42.4)	OR 0.90 (0.52, 1.55)	
Kim 2014	3/9 (33.3)	9/32 (28.1)	OR 1.28 (0.26, 6.24)	
Nardi 2015	3/96 (3.1)	8/130 (6.2)	OR 0.49 (0.13, 1.91)	
Rowell 2011	46/210 (22)	76/245 (31)	OR 0.62 (0.41, 0.95)	
Synder 2009	24/60 (40)	43/74 (58.1)	OR 0.48 (0.24, 0.96)	
Stanworth 2016	25/206 (12.1)	26/92 (28.3)	OR 0.35 (0.19, 0.65)	
Mortality, 30-days 10 observation studies N = 2849	631/1801 (35)	499/1048 (47.6)	OR 0.47 (0.31, 0.71)	*Favours high ratio* *p* = 0.0004 Substantial heterogeneity I^2 = 81% (*p* <0.00001)
Borgman 2011	145/422 (34.4)	109/237 (46)	OR 0.61 (0.44, 0.85)	
Holcomb 2008	78/151 (51.7)	40/83 (48.2)	OR 1.15 (0.67, 1.96)	
Kim 2014	22/68 (32.4)	14/32 (43.8)	OR 0.61 (0.26, 1.46)	
Magnotti 2011	25/66 (37.9)	22/37 (59.5)	OR 0.42 (0.18, 0.95)	
Nardi 2015	13/96 (13.5)	26/130 (20)	OR 0.63 (0.30, 1.29)	
Peiniger 2011	203/445 (45.6)	104/167 (62.3)	OR 0.51 (0.35, 0.73)	
Rowell 2011	84/210 (40)	108/245 (44.1)	OR 0.85 (0.58, 1.23)	
Sharpe 2012	20/69 (29)	15/26 (57.7)	OR 0.30 (0.12, 0.76)	
Teixeira 2009	30/115 (26.1)	56/62 (90.3)	OR 0.04 (0.01, 0.10)	
Van 2010	11/159 (7)	5/29 (17.2)	OR 0.36 (0.11, 1.12)	
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. Some studies include combat/military patients which, while not directly generalisable to the population, can provide some guidance for Australian trauma patients. Other included studies were conducted in civilian populations in a wide range of ages which is reflective of the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. Studies conducted in Australia are directly applicable. Studies conducted in UK and Europe may be applicable to the Australian healthcare context.				
Additional comments				
Authors conclusions: Randomised data have not shown a mortality benefit from higher ratios. Additionally, low quality observational evidence demonstrates a survival benefit in patients receiving higher transfusion ratios. However, results should be interpreted with extreme caution as research is limited by small sample sizes, lack of clinical trials and high probability of confounding. Larger prospective RCTs with several thousand patients would be required. *List of included relevant studies* RCTs: Holcomb 2015, Nascimento 2013 Observational: Vulliamy 2017, Balvers 2017, Haltmeier, Stanworth 2016, Hagiwara 2016 , Bui 2016, Baysinger 2016, Nardi 2015, Glaser 2015, Mitra 2014, Kutcher 201, Kim 2014, Kahn 2014, Hardin 2014, Kutcher 2013, Kudo 2013, Holcomb 2013,				

STUDY DETAILS: da Luz 2019
Halmin 2013, Sisak 2012, Sharpe 2012, Brown 2012, Wafaisade 2011, Spinella 2011, Simmons 2011, Sambasivan 2011, Rowell 2011, Peiniger 2011, Magnotti 2011, Lustenberger 2011, Holcomb 2011, Davenport 2011, Brown 2011, Borgman 2011, Van 2010, Mitra 2010, Zink 2009, Teixeira 2009, Synder 2009, Shaz 2009, Riskin 2009, Perkins 2009, Duchesne 2009, Dente 2009, Cotton 2009, Stinger 2008, Sperry 2008, Scalea 2008, Maegele 2008, Kashuk 2008, Holcomb 2008, Gunter 2008, Duchesne 2008, Borgman 2007

CI, confidence interval; FFP, fresh frozen plasma; OR, odds ratio; PLT, platelet; RBC, red blood cells; RCT, randomised controlled trial; SD, standard deviation; UK, United Kingdom; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Kinslow 2020			
Citation			
Kinslow K, McKenney M, Boneva D, Elkbuli A. Massive transfusion protocols in paediatric trauma population: a systematic review. Transfusion Medicine. 2020; 30: 333-342.			
Affiliation/Source of funds			
Author affiliations: All authors affiliated with the Department of Surgery, Kendall Regional Medical Center, Miami, Florida. MM and DB affiliated with the University of South Florida, Tampa, Florida. Details on funding are not provided. The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of observational studies	I-III	US	Paediatric trauma
Intervention		**Comparator**	
High ratios of blood products: *Edwards 2015 ≥1; 1:1 FFP:RBC *Nosanov 2013 >1:1 FFP:RBC; also >1:3 Platelet:RBC investigated separately *Noland 2018 1:1 FFP:RBC *Cunningham 2019 ≥1:1 Plasma:RBC *Synder 2009 <1:2 FFP:RBC *Butler 2019 >1:1 FFP:pRBC; also ≥1:2 Platelet:pRBC investigated separately		Other ratios of blood products: *Edwards 2015 ≤ 0.4, 0.4-0.6, 0.6-0.8, *Nosanov 2013 <1:2 and 1:2-1:1 FFP:RBC; also 1:6 and 1:6-1:3 Platelet:RBC investigated separately *Noland 2018 2:1 and 3:1 FFP:RBC *Cunningham 2019 <1:2, ≥1:2-<1:1 Plasma:RBC *Synder 2009 <1:2 FFP:RBC *Butler 2019 <1:2 and 1:2-1:1 FFP:pRBC; also no platelets and <1:2 Platelets:pRBC investigated separately	
Population characteristics			
Paediatric trauma patients with various injury severity scores. One study (Edwards 2015) in combat population with predominately penetrative trauma. All other studies had majority blunt trauma.			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, Google Scholar, Cochrane Library, Embase, Wiley Online Library and OVID. No restrictions on date of publication were included. Authors do not provide details of search dates (e.g. inception to 1 January 2019)		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* No risk of bias for included studies was performed. Authors acknowledge limitations of individual studies, primarily differences in definitions in massive transfusion in paediatric patients.			

STUDY DETAILS: Kinslow 2020				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (p-value)**
High ratios versus lower ratios				
Mortality, overall 6 studies, N = 1025 Noland 2018 Cunningham 2019 Butler 2019 Nosanov 2013 Edwards 2015 Synder 2009	 2:1 ratio: 10/35 (29) 3:1 ratio: 14/34 (39) Medium ratio: 42/176 (24) High ratio: 15/126 (12) Medium ratio: 97/215 (45.1) High ratio: 46/136 (33.8) Medium ratio: 6/43 (14) High ratio: 11/34 (32.6) NR (18) 24/60 (40)	 1:1 ratio: 6/39 (15) Low ratio: 38/163 (23) Low ratio: 104/232 (44.8) Low ratio: 2/15 (13.3) NR (8) 43/74 (58)	NR	NR Significant improvement in paediatric mortality with high ratio blood products No significant association of high ratio transfusions with improved mortality outcomes
Mortality, 24 hours 1 study, N = NR Butler 2019	NR	NR	NR	NR Significant improvement with high ratios FFP:RBC
High ratios versus lower ratios				
DVT 1 study, N = NR Butler 2019	Medium ratio: 10/215 (4.7) High ratio: 9/136 (6.6)	Low ratio: 6/232 (2.6)	NR	NR 2:1 FFP:pRBC associated with 6.9x increased risk for development of DVT compared to lower ratios
Pneumonia 1 study, N = NR Butler 2019	NR	NR	NR	NR >2:1 Platelet:pRBC associated with 23.6x increased risk for development of pneumonia compared to lower ratios
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. Authors do not provide sufficient details regarding individual study findings making it difficult to confidently apply to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context. Authors do not provide details of study locations or sufficient details regarding individual study findings making it difficult to confidently apply to the Australian healthcare context.				
Additional comments				
Authors conclusions: Existing evidence trends in the direction of supporting balanced approaches in paediatric populations.				

STUDY DETAILS: Kinslow 2020
This review is a narrative review only with a lack of individual study data limiting the ability to make sound conclusions. *List of relevant included studies:* Butler 2019, Cunningham 2019, Edwards 2015, Noland 2018, Nosanov 2013, Synder 2009

CI, confidence interval; DVT, deep vein thrombosis; FFP, fresh frozen plasma; NR, not reported; pRBC, packed red blood cells; RBC red blood cell; RR, relative risk; SD, standard deviation; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Meneses 2020			
Citation			
Meneses E, Boneva D, McKenney M & Elkbuli A. Massive transfusion protocol in adult trauma population. American Journal of Emergency Medicine. 2020; 38: 2661-2666.			
Affiliation/Source of funds			
Author affiliations: All authors affiliated with Department of Surgery, Division of Trauma and Surgical Critical Care, Kendall Regional Medical Center, Miami, Florida, USA; DB and MM affiliated with Department of Surgery, University of South Florida, Tampa, Florida, USA. The authors declared that the study received no funding. The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of observational studies	I-III	Not reported	Trauma
Intervention		**Comparator**	
High ratios of blood products		Lower ratios of blood products	
Population characteristics			
Adult trauma patients age 15+ years as defined by the American College of Surgeons. Individual study characteristics not described.			
Length of follow-up		**Outcomes measured**	
PubMed database searched from database inception to July 2020		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* No risk of bias for included studies conducted or considered by the authors.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
High ratio versus Low ratio				
Mortality 11 studies Holcomb 2015 Duchesne 2008 Teixeria 2009 Kashuk 2008 Scalea 2008 Shaz 2010 Dente 2009 Borgman 2007	NR 51/365 (41)	NR 50/441 (11.5)	NR	Authors provide a narrative summary of studies. No data provided.

STUDY DETAILS: Meneses 2020				
Sperry 2008 Holcomb 2008 Maegele 2008				
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. Authors provide no study characteristics making is difficult to determine if the study's adult trauma population is generalisable to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context. The authors provide no study characteristics regarding locations and therefore it is not reasonable to conclude the applicability to the Australian healthcare context.				
Additional comments				
Authors conclusions: A balanced transfusion of FFP:platelet:PRBC ranging between 1:1:1 and 1:1:2 has been associated with a decreased mortality as well as other complications. Early initiation of an MTP and faster timing of product delivery is also associated with less organ failure. *List of relevant included studies:* Holcomb 2015, Duchesne 2008, Teixeria 2009, Kashuk 2008, Scalea 2008, Shaz 2010, Dente 2009, Borgman 2007, Sperry 2008, Holcomb 2008, Maegele 2008				

CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; MD, mean difference; MTP, massive transfusion protocol; NR, not reported; PP, per-protocol; PRBC, packed red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Richie 2020			
Citation			
Ritchie DT, Pilbrook FGA, Leadbitter S, Kokwe KN, Meehan E, et al. Empirical transfusion strategies for major hemorrhage in trauma patients: a systematic review. Journal of Trauma and Acute Care Surgery. 2020; 88(6): 855-865			
Affiliation/Source of funds			
Author affiliations: all authors affiliated with the School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom. The authors declared no funding or conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of RCTs	I-II	North America, UK, Iran	Trauma
Intervention		**Comparator**	
High ratios blood product Holcomb 2015: 1:1:2 Nascimento 2013: 1:1:1		Lower ratios blood product Holcomb 2015: 1:1:1 Nascimento 2013: laboratory guided	
Population characteristics			
Trauma patients			
Length of follow-up		**Outcomes measured**	
Databases searched: Embase, Medline, CINAHL and Web of Science. Searches were conducted May 2019. Date limits not specified.		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and ***may not*** provide an accurate and comprehensive summary of the available studies that address the question of interest.			

STUDY DETAILS: Richie 2020				
Risk of bias of included studies: the overall risk of bias for included studies was judged by the review authors to be high. There were concerns with attrition bias due to incomplete reporting.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
High ratio blood product versus Lower ratio blood product				
Mortality, 24 hours 1 study, N = 680 Holcomb 2015	 58/342 (17.0)	 43/338 (12.8)	 RR 1.33 (0.93, 1.92)	 No significant difference
Mortality, 28/30 days 2 studies, N = 758 Holcomb 2015 Nascimento 2013	NR 89/342 (26.0) 11/37 (29.7)	NR 75/338 (22.2) NR	NR RR 1.17 (0.90, 1.53) NR	NR No significant difference NR
Hospital-free days, 2 studies, N = 758 Holcomb 2015 Nascimento 2013	 Median (IQR) 0 (0-16) 0 (0-15)	 Median (IQR) 1 (0-17) NR	 NR NR	 No significant difference
Thromboembolic events 2 studies, N = 758 Holcomb 2015 Nascimento 2013	 61/342 (17.84) 37 (8.1)	 62/338 (18.34) NR	 0.97 (0.71, 1.34) NR	 No significant difference NR
MOF 1 study, N = 680 Holcomb 2015	 15/342 (4.39)	 20/338 (5.29)	 0.74 (0.39, 1.42)	 No significant difference
Sepsis 1 study, N = 680 Holcomb 2015	 91/342 (26.61)	 99/338 (29.29)	 0.91 (0.71, 1.16)	 No significant difference
Volume, 24 hours 1 study, N = 680 Holcomb 2015 RBC Plasma Platelets CRYO Crystalloids Colloids	 9 (6, 16) 5 (2, 10) 6 (0, 12) 0 (0, 9) 6.6 (3.5, 10.5) 0 (0, 0.3)	 9 (5, 15) 7 (3, 13) 12 (6, 18) 0 (0, 0) 6.3 (3.8, 9.5) 0 (0, 0.3)		 No significant difference No significant difference No significant difference No significant difference No significant difference
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats				
Additional comments				
List of relevant included studies:				

STUDY DETAILS: Richie 2020
Holcomb 2015, Nascimento 2013

CI, confidence interval; CRYO, cryoprecipitate; ITT, intention-to-treat; MD, mean difference; MOF, multiple organ failure; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation, UK, United Kingdom

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Rodriguez 2020			
Citation			
Rodriguez, HO., Rios, F., Rubio, C., Arsanios, DM., Herazo, F., Beltran, LM., Garcia, P., Cifuentes, A., Munoz, J. & Polania, J. 2020. Mortality in civilian trauma patients and massive blood transfusion treated with high vs low plasma: red blood cell ratio. Systematic review and meta-analysis. *Colombian Journal of Anesthesiology, 48*(3), 126-137. http://dx.doi.org/10.1097/CJ9.0000000000000161			
Affiliation/Source of funds			
The authors declared they received no external funding. *Author affiliations:* School of Medicine, Universidad de La Sabana, Chía, Colombia (HOR, FR, DMA, AFH, LMB, PC, AC, JM, JP) Clínica Universidad de La Sabana, Chía, Colombia (FR)., Epidemiology Postgraduate Program, Facultad de Medicina, Universidad de la Sabana, Chía, Colombia (CR). The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of observational studies	I-III	Individual study locations not included	Trauma
Intervention		**Comparator**	
High RBC:FFP ratio		Low RBC:FFP ratio	
Population characteristics			
Trauma patients following a massive bleed			
Length of follow-up		**Outcomes measured**	
Databases searched: Medline, Medline In-Process & other non-indexed Citations, MEDLINE daily Update, EMBASE, PsycINFO and Lilacs from January 2007- June 2019		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:*			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
High FFP:RBC ratio vs low FFP:RBC ratio				
30-day mortality N = 11052 (22 studies)	NR	NR	OR 0.79 (0.71, 0.87)	I^2 = 86.3%
Holcomb 2013 (N = 418)	NR	NR	OR 1.99 (1.32, 2.98)	
Sperry 2008 (N = 415)	NR	NR	OR 0.73 (0.45, 1.20)	
Maegele 2008 (N = 713)	NR	NR	OR 0.51 (0.36, 0.71)	
Gunter 2008 (N = 259)	61/119 (52)	53/140 (37)	OR 0.43 (0.24, 0.76)	
Teixeira 2009 (N = 383)	NR	NR	OR 0.37 (0.26, 0.60)	
Dente 2009 (N = 73)	NR	NR	OR 0.56 (0.20, 1.55)	

STUDY DETAILS: Rodriguez 2020				
Zink 2009 (N = 452)	NR	NR	OR 0.43 (0.22, 0.83)	
Mitra 2010 (N = 331)	NR	NR	OR 0.93 (0.49, 1.74)	
Shaz 2010 (N = 190)	NR	NR	OR 1.18 (0.66, 2.10)	
Spoerke 2011 (N = 529)	NR	NR	OR 0.39 (0.25, 0.62)	
Rowell 2011 (N = 704)	NR	NR	OR 0.71 (0.53, 0.96)	
Peiniger 2011 (N = 1250)	NR	NR	OR 2.11 (1.65, 2.69)	
Borgman 2011 (N = 659)	NR	NR	OR 0.61 (0.44, 0.85)	
Spinella 2011 (N = 461)	NR	NR	OR 0.74 (0.40, 1.35)	
Wafaisade 2011 (N = 1362)	NR	NR	OR 0.66 (0.51, 0.85)	
Sharpe 2012 (N = 135)	NR	NR	OR 0.46 (0.23, 0.94)	
Nascimento 2013 (N = 69)	NR	NR	OR 4 (1.03, 16.3)	
Kudo 2014 (N = 15)	NR	NR	OR 0.8 (0.10, 6.35)	
Kim 2014 (N = 100)	NR	NR	OR 0.61 (0.26, 1.46)	
Peralta 2015 (N = 77)	NR	NR	OR 0.2 (0.07, 0.55)	
Holcomb 2015 (N = 680)	NR	NR	OR 0.81 (0.57, 1.15)	
Endo 2018 (N = 1777)	High ratio: 76/237 (32.1)	Low ratio: 300/814 (36.9) Intermediate: 226/726 (31.1)	OR 0.85 (0.60, 1.21)	
Mortality within 24 hr N = 10840 (27 studies)	NR	NR	OR 0.67 (0.60, 0.75)	I^2 = 91.9%
Holcomb 2013 (N = 418)	NR	NR	OR 1.81 (0.16, 2.81)	
Sperry 2008 (N = 415)	NR	NR	OR 0.28 (0.10, 0.80)	
Duchesne 2008 (N = 135)	NR	NR	OR 0.05 (0.02, 0.13)	
Maegele 2008 (N = 713)	NR	NR	OR 0.34 (0.22, 0.41)	
Kashuk 2008 (N = 140)	NR	NR	OR 0.54 (0.27, 1.06)	
Snyder 2009 (N = 134)	NR	NR	OR 0.48 (0.24, 0.96)	
Dente 2009 (N = 73)	NR	NR	OR 0.37 (0.11, 1.23)	
Zink 2009 (N = 452)	NR	NR	OR 0.07 (0.01, 0.55)	
Mitra 2010 (N = 331)	NR	NR	OR 0.32 (0.10, 1.08)	
Shaz 2010 (N = 190)	NR	NR	OR 1.8 (0.92, 3.54)	
Lustenberger (N = 229)	NR	NR	OR 0.08 (0.04, 0.16)	
Spoerke 2011 (N = 529)	NR	NR	OR 0.29 (0.16, 0.52)	
Rowell 2011 (N = 704)	NR	NR	OR 0.54 (0.38, 0.76)	
Peiniger 2011 (N = 1250)	NR	NR	OR 3.29 (2.52, 4.29)	
Magnotti 2011 (N = 103)	NR	NR	OR 0.39 (0.17, 0.89)	
Borgman 2011 (N = 659)	NR	NR	OR 0.47 (0.33, 0.68)	
Wafaisade 2011 (N = 1362)	NR	NR	OR 0.51 (0.36, 0.73)	
Brown 2012 (N = 604)	NR	NR	OR 0.37 (0.14, 0.95)	
Duchesne 2013 (N = 451)	311/365 (85.2)	59/86 (68.6)	OR 038 (0.22, 0.65)	
Simms 2014 (N = 151)	NR	NR	OR 0.19 (0.08, 0.45)	
Guirdry 2013 (N = 234)	122/156 (78.4)	58/78 (74.7)	OR 0.63 (0.35, 1.14)	
Kudo 2014 (N = 15)	NR	NR	OR 1 (0.11, 8.95)	
Kim 2014 (N = 100)	NR	NR	OR 0.08 (0.02, 0.39)	
Peralta 2015 (N = 77)	14/31 (46.7)	29/46 (63.6)	OR 0.15 (0.05, 0.45)	
Stanworth 2016 (N = 298)	NR	NR	OR 0.35 (0.19, 0.65)	
Holcomb 2015 (N = 680)	NR	NR	OR 0.71 (0.47, 1.09)	
Biasi 2011 (N = 393)			OR 1.54 (0.93, 2.54)	

STUDY DETAILS: Rodriguez 2020				
	5-9u RBC: 54/308 (25.9) >9u RBC: 148/307 (48.2)	1-4u RBC: 99/320 (30.9)		
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context				
Additional comments				
Authors conclusions: The use of high FFP:RBC ratio in civilian trauma patients and massive transfusion was associated with a lower mortality risk in the first 24hours and at 30 days when the observational trials were assessed. *Included studies:* Holcomb 2008, Sperry 2008, Duchesne 2008, Maegele 2008, Gunter 2008, Kashuk 2008, Teixeira 2009, Snyder 2009, Dente 2009, Zink 2009, Mitra 2010, Shaz 2010, Lustenberg 2011, Spoerke 2011, Rowell 2011, Peiniger 2011, Magnotti 2011, Borgman 2011, Biasi 2011, Spinella 2011, Wafaisade 2011, Brown 2012, Sharpe 2012, Duchesne 2013, Simms 2014, Guidry 2013, Nascimento 2013, Kudo 2014, Kim 2014, Peralta 2015, Stanworth 2016, Holcomb 2015, Endo 2018				

CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; MD, mean difference; NR, not reported; OR, odds ratio; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation;

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Wirtz 2020			
Citation			
Wirtz MR, Schalkers DV, Gosling JC & Juffermans NP. The impact of blood product ratio and procoagulant therapy on the development of thromboembolic events in the severely injured hemorrhaging trauma patients. Transfusion. 2020; 60: 1873-1882			
Affiliation/Source of funds			
Author affiliations: MRW, DVS and NPJ affiliated with Department of Intensive Care and MRW affiliated with Trauma Unit, Department of Surgery, Amsterdam University Medical Centers, Amsterdam, The Netherlands; JCG affiliated with Trauma Unit, Department of Trauma Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands The authors declared no conflicts of interest. Details on funding are not provided.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of RCTs and observational studies	I-II/III	USA, Europe, Asia, Canada, Global	Trauma
Intervention		**Comparator**	
High ratio blood products (FFP or PLT:RBC)		Lower ratio blood products (FFP or PLT:RBC)	
Population characteristics			
Patients ≥16 years with severe trauma (ISS ≥16) resulting in haemorrhage			
Length of follow-up		**Outcomes measured**	
Databases searched: Medline, PubMed and Embase. In addition, ongoing trials searched through www.controlled-trials.com and www.clinicaltrials.gov Search dates not provided		Thromboembolic events	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review.			

STUDY DETAILS: Wirtz 2020				
Risk of bias of included studies: Overall, the authors judged the included observational studies to be of moderate quality (based on the Newcastle-Ottawa scale). Overall quality of RCTs was also judged to be of moderate quality by the authors with performance and detection bias being of high risk due to the difficulty of blinding for transfusion status of patients.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**Low ratio** **n/N (%)** **Mean ± SD**	**High ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Low ratio FFP:RBC versus High ratio FFP:RBC				
Thromboembolic events (Risk of) 3 studies, N = 962	66/433 (15.2)	82/529 (15.5)	OR 0.66 (0.28, 1.56)	No significant difference *p* = 0.34 No significant heterogeneity
Guidry 2013 Holcomb 2015[b] Zielinski 2013	3/78 (3.9) 62/338 (18.3) 1/17 (5.9)	14/156 (9) 61/342 (17.8) 7/31 (22.6)	OR 0.41 (0.11, 1.46) OR 1.03 (0.70, 1.53) OR 0.21 (0.02, 1.91)	I^2 = 45% (*p* = 0.16)
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. The authors did not provide sufficient information regarding trauma injury (e.g., combat, civilian, etc.) therefore making it difficult to determine the generalisability of trauma patients with that of the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The majority of studies were carried out in the USA; however, findings could be sensible translated to the Australian healthcare context. Studies in Europe are more easily applicable to the Australian healthcare context.				
Additional comments				
Authors conclusions: incidence of thromboembolic events in severely injured trauma patients was 10%. No significant difference between the ratio of blood products and the risk of thromboembolic events. *List of relevant included studies:* Guidry 2013, Holcomb 2015, Zielinski 2013				

CI, confidence interval; FFP, fresh frozen plasma; ISS, injury severity score; MD, mean difference; OR, odds ratio; PLT, platelet; RBC, red blood cell, RCT, randomised controlled trial; SD, standard deviation; USA< United States of America

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Numbers reported by Wirtz are different to that of Klienveld.

STUDY DETAILS: Kleinveld 2021			
Citation			
Kleinveld DJB, van Amstel RBE, Wirtz MR, Geeraedts LMG, Goslings JC, et al. Platelet-to-red blood cell ratio and mortality in bleeding trauma patients: a systematic review and meta-analysis. Transfusion. 2021; 61: S243-S251.			
Affiliation/Source of funds			
Author affiliations: Department of Intensive Care Medicine, Laboratory of Experimental Intensive Care and Anesthesiology, Department of Trauma, Department of Anesthesiology, Amsterdam UMC; Department of Trauma Surgery, OLVG Hospital, Amsterdam; Department of Intensive Care, OLVG Hospital, Amsterdam. *Funding* support was provided solely from institutional and/or departmental sources. *Conflicts of interest*: Dr Hollmann is Executive Section Editor Pharmacology with Anesthesiology and Section Editor Anesthesiology with the Journal of Clinical Medicine. He has received research funding from ZonMW, STW, SCA, ESA, Eurocept BV, Edwards Life Sciences. Dr Hollmann served as consultant for Eurocept BV and ECHO BV and received speakers fees from CSL Behring and BBraun. All other authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of RCTs (5)	I-II	Not reported	Trauma

STUDY DETAILS: Kleinveld 2021				
Intervention		**Comparator**		
High ratios of plasma or platelet:RBC		Low ratios of plasma or platelet:RBC		
Population characteristics				
Trauma patients (≥16 years)				
Length of follow-up		**Outcomes measured**		
Databases searched: PubMed, Medline and Embase. In addition, Clinicaltrials.gov and controlled-trials.com were searched for ongoing trials. **Citations published from database inception to October 2020**		Mortality, 24-hours & 30-days Thromboembolic events Organ failure Correction of coagulopathy		
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The overall quality of the studies was judged by the review authors to be moderate. All but one RCT scored high risk of bias due to the impossibility of blinding of personnel to the allocation of treatment strategy.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (p-value)**
High ratio platelet:RBC versus Low ratio platelet:RBC				
Mortality, 24 hours 5 studies, N = 1757	116/862 (13.5)	166/895 (18.5)	OR 0.69 (0.53, 0.89)	*Favours high ratio* *p* = 0.005 Moderate heterogeneity
Nascimento 2013	8/37 (21.6)	3/32 (9.4)	OR 2.67 (0.64, 11.07)	I^2 = 41% (*p* = 0.15)
Holcomb 2015	43/338 (12.7)	58/342 (17.0)	OR 0.71 (0.47, 1.09)	
Gonzalez 2016	4/56 (7.1)	12/55 (21.8)	OR 0.28 (0.08, 0.92)	
Sperry 2018	32/230 (13.9)	60/271 (22.1)	OR 0.57 (0.35, 0.91)	
Baksaas-Aasen 2020	29/201 (14.4)	33/195 (16.9)	OR 0.83 (0.48, 1.42)	
Mortality, 30-days 5 studies, N = 1757	194/862 (22.5)	243/895 (27.2)	OR 0.78 (0.63, 0.98)	*Favours high ratio* *p* = 0.003 Moderate heterogeneity
Nascimento 2013	11/37 (29.7)	3/32 (9.4)	OR 4.09 (1.03, 16.29)	I^2 = 47% (*p* = 0.11)
Holcomb 2015	75/338 (22.2)	89/342 (26.0)	OR 0.81 (0.57, 1.15)	
Gonzalez 2016	7/56 (12.5)	8/55 (14.5)	OR 0.84 (0.28, 2.50)	
Sperry 2018	51/230 (22.2)	88/271 (32.5)	OR 0.59 (0.40, 0.89)	
Baksaas-Aasen 2020	50/201 (24.9)	55/195 (28.2)	OR 0.84 (0.54, 1.32)	
Thromboembolic events 3 studies, N = 1187	65/595 (10.9)	70/592 (11.8)	OR 0.91 (0.64, 1.31)	No significant difference *p* = 0.63 Moderate heterogeneity I^2 = 40% (*p* = 0.19)
Holcomb 2015	39/338 (11.5)	37/342 (10.8)	OR 1.08 (0.67, 1.73)	
Gonzalez 2016	9/56 (16.1)	6/55 (10.9)	OR 1.56 (0.52, 4.73)	
Baksaas-Aasen 2020	17/201 (8.5)	27/195 (13.8)	OR 0.57 (0.30, 1.09)	
Multiple organ dysfunction syndrome 5 studies, N = 1684	309/825 (37.5)	308/859 (35.9)	OR 1.24 (0.94, 1.64)	No significant difference *p* = 0.13 No heterogeneity I^2 = 0% (*p* = 0.93)

STUDY DETAILS: Kleinveld 2021				
Nascimento 2013	1/37 (2.7)	0/32	OR 2.67 (0.11, 67.89)	
Holcomb 2015	20/338 (5.9)	15/342 (4.4)	OR 1.37 (0.69, 2.73)	
Gonzalez 2016	2/56 (3.6)	3/55 (5.5)	OR 0.64 (0.10, 4.00)	
Sperry 2018	145/230 (63.0)	156/271 (57.6)	OR 1.26 (0.88, 1.80)	
Baksaas-Aasen 2020	141/164 (86.0)	134/159 (84.3)	OR 1.14 (0.62, 2.11)	
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population but could be sensibly applied. Although not described, some populations may be in combat areas which may not be directly generalisable, however, the nature of trauma could be applied.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The authors do not provide details of study locations which may influence the applicability.				
Additional comments				
Authors conclusions: **ResusCitation with a high compared to low platelet:RBC ratio improves early and late mortality in patients with traumatic bleeding. The high platelet:RBC ratio did not influence the occurrence of organ failure. The optimal ratio for platelet:RBC and its effect on platelet function in traumatic bleeding remains to be determined.** *List of relevant included studies:* Baksaas-Aasen 2020, Gonzalez 2016, Holcomb 2015, Nascimento 2013, Sperry 2018				

CI, confidence interval; OR, odds ratio; RBC, red blood cells; RCT, randomised controlled trial; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Phillips 2021			
Citation			
Phillips AR, Tran L, Foust JE & Liang NL. Systematic review of plasma/packed red blood cell ratio on survival in ruptured abdominal aortic aneurysms. Journal of Vascular Surgery. 2021; 73(4): 1438-1444.			
Affiliation/Source of funds			
Author affiliations: ARP, LT and NLL affiliated with the Division of Vascular Surgery, Department of Surgery, University of Pittsburgh Medical Center; JEF affiliated with the University of Pittsburgh The research was supported in part by the grand 5T32HL0098036 from the National Heart, Lung, and Blood Institute for ARP. The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of observational studies (7)	I-III	Henriksson 2012 - Sweden Not reported for other studies	Single centre, surgical
Intervention		**Comparator**	
High FFP/RBC ratio		Lower FFP/RBC ratio	
Population characteristics			
Adults with a diagnosis of AAA.			
Length of follow-up		**Outcomes measured**	
Database searches: PubMed and Embase (from database inception to September 2019), Cochrane Central Register of Controlled Trials (from January 1999 to September 2019) and Clinicaltrials.gov (from 2000 to September 2019)		Mortality	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.			

STUDY DETAILS: Phillips 2021				
Risk of bias of included studies: The overall risk of bias by the review authors was judged to be serious. A significant amount of bias in the overall judgement resulted from confounding. The presence of confounding in observational studies is difficult to account for and will often be inherent to the Study design.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**High ratio** **n/N (%)** **Mean ± SD**	**Low ratio** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
High ratio FFP:pRBC versus Low ratio FFP:pRBC [b]				
Mortality, 30-days 4 studies N = 580	NR	NR	NR	
Mell 2010	13/87 (15)	16/41 (39)	OR 4.23 (1.23, 14.49)	*p* < 0.03
Johansson 2007	17/50 (34)	46/82 (56)	NR	*p* = 0.02
Johansson 2008	16/64 (25)	46/82 (56)	NR	*p* < 0.01
Henriksson 2012	20/100 (20)	23/74 (31)	NR	*p* = 0.111
Mortality 2 studies, N = 101				*No significant difference*
Hall 2013	21/68 (31)	6/21 (28)	NR	*p* > 0.05
Tadlock 2010	1/4 (25)	6/8 (75)	NR	*p* = 0.222
High tRBC:FFP versus Low tRBC:FFP				
Mortality, in-hospital 1 study				*No significant difference*
Kauvar 2011	19/39 (49)	19/48 (40)	NR	*p* = 0.39
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. Locations of all studies was not reported making it difficult to know the direct applicability to the Australian healthcare context.				
Additional comments				
Authors conclusions: The use of a higher FFP:pRBC ratio will confer a survival benefit for patients undergoing open surgical repair for ruptured AAAs. However, the included studies had a severe risk of bias, and the quality of evidence was very low. Overall, further research is warranted. *List of relevant included studies:* Mell 2010, Kauvar 2011, Hall 2013, Johansson 2007, Johansson 2008, Tadlock 2010, Henriksson 2012				

AAA, abdominal aortic aneurysm; CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; OR, odds ratio; pRBC, packed red blood cells; SD, standard deviation; tRBC, total red blood cells

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

b. Data sourced from primary studies.

STUDY DETAILS: Rijnhout 2021
Citation
Rijnhout TWH, Duijst J, Noorman F, Zoodsma M, van Waes OJF, et al. Platelet to erythrocyte transfusion ratio and mortality in massively transfused trauma patients. A systematic review and meta-analysis.

STUDY DETAILS: Rijnhout 2021			
Affiliation/Source of funds			
Author affiliations: Department of Surgery (T.W.H.R., R.H.), Alrijne Medical Center, Leiderdorp; Trauma Research Unit, Department of Surgery (T.W.H.R., O.J.F.vW., M.H.J.V., R.H.), Erasmus MC, University Medical Center Rotterdam, Rotterdam; Department of Anesthesiology and Pain Medicine (J.D.), Maastricht University Medical Center+, Maastricht; Military Blood Bank (F.N., M.Z.), Defense Healthcare Organization (R.H.), Ministry of Defense, Utrecht; and Department of Surgery (R.H.), Leiden University Medical Center, Leiden, The Netherlands. The study was supported by the Dutch Department of Defense and the Dutch Army Health Insurance Foundation (SZVK). The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of RCTs (2) and observational studies (10)	I-II/III	NR	Trauma, military and civilian
Intervention		**Comparator**	
High ratio blood products		Lower ratio blood products	
Population characteristics			
Trauma patients (by either blunt or penetrating trauma) with an ISS ranging between 26 and 37			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, CINAHL, Embase, Cochrane **Citations published between database inception and 21 January 2021**		Mortality Transfusion	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* the overall risk of bias for included RCTs was judged by the review authors to be high based on several components including randomisation processes, deviations, missing outcome and selective reporting. Non-RCTs were judged as critical risk mainly due to confounding and selection bias.			
RESULTS:			

Outcome No. patients (No. trials)	**High ratio n/N (%) Mean ± SD**	**Low ratio n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance* *p*-value Heterogeneity[a] I^2 (*p*-value)**
High PLT:RBC ≥0.7 versus Low PLT:RBC <0.7				
Mortality, 1-6 hours 2 studies, N = 668	5/143 (3.5)	63/525 (12)	OR 0.18 (0.07, 0.49)	*Favours high ratio* *p* = 0.0007 No significant heterogeneity I^2 = 0% (*p* = 0.78)
Brown 2012	2/116 (1.7)	49/488 (10.0)	OR 0.16 (0.04, 0.66)	
Simms 2014	3/27 (11.1)	14/37 (37.8)	OR 0.21 (0.05, 0.81)	
High PLT:RBC ≥0.3 versus Low PLT:RBC <0.3				
Mortality, 24 hours 2 studies, N = 413	36/389 (9.3)	66/124 (53.2)	OR 0.12 (0.08, 0.21)	*Favours high ratio* *p* < 0.00001 No significant heterogeneity I^2 = 0% (*p* = 0.59)
Lustenberger 2011	16/163 (9.8)	33/66 (50.0)	OR 0.11 (0.05, 0.22)	
Shaz 2010	20/126 (15.9)	33/58 (56.9)	OR 0.14 (0.07, 0.29)	
High PLT:RBC ≥0.5 versus Low PLT:RBC <0.5				
Mortality, 24 hours 5 studies, N = 2143	196/980 (20)	384/1163 (33.0)	OR 0.46 (0.28, 0.76)	*Favours high ratio* *p* = 0.002 Substantial heterogeneity I^2 = 75% (*p* = 0.003)
Cap 2017	7/70 (10)	76/344 (22.1)	OR 0.39 (0.17, 0.89)	

STUDY DETAILS: Rijnhout 2021				
Inaba 2010	100/409 (24.4)	141/248 (56.9)	OR 0.25 (0.18, 0.34)	
Perkins 2011	45/284 (15.8)	16/85 (18.8)	OR 0.81 (0.43, 1.52)	
Rowell 2011 (blunt)	29/145 (20)	93/310 (30)	OR 0.58 (0.36, 0.94)	
Rowell 2011 (penetrating)	15/72 (20.8)	58/176 (33.0)	OR 0.54 (0.28, 1.03)	
Mortality, 28/30 days 3 studies, N = 1117	88/287 (30.7)	305/830 (36.7)	OR 0.68 (0.50, 0.91)	*Favours high ratio* *p* = 0.01 No significant heterogeneity I^2 = 0% (*p* = 0.71)
Cap 2017	13/70 (18.6)	99/344 (28.8)	OR 0.56 (0.30, 1.08)	
Rowell 2011 (blunt)	54/145 (37.2)	136/310 (43.9)	OR 0.76 (0.51, 1.14)	
Rowell 2011 (penetrating)	21/72 (29.2)	70/176 (39.8)	OR 0.62 (0.35, 1.13)	
RBC transfusion 4 studies, N = 1486				*Favours high ratio* *p* = 0.06
Cap 2017	18 (8.3)	16 (7.4)	MD 2.00 (-0.10, 4.10)	No significant heterogeneity I^2 = 0% (*p* = 0.74)
Perkins 2011	29 (35.8)	27 (31.7)	MD 2.00 (-5.29, 9.92)	
Rowell 2011 (blunt)	18.2 (8.6)	17.7 (9.8)	MD 0.50 (-1.27, 2.27)	
Rowell 2011 (penetrating)	20.9 (14.2)	19.2 (10.8)	MD 1.70 (-1.95, 5.35)	
Plasma transfusion 2 studies, N = 783				*Favours high ratio* *p* = 0.01 Mild heterogeneity I^2 = 37% (*p* = 0.71)
Cap 2012	12 (3.8)	9 (6)	MD 3.00 (1.91, 4.09)	
Perkins 2011	18.7 (29.8)	12 (21.1)	MD 6.70 (1.03, 12.37)	
High PLT:RBC ≥1 versus Low PLT:RBC <0.5-1				
Mortality, 24 hours 3 studies, N = 1497	149/704 (21.1)	203/793 (25.6)	OR 0.81 (0.30, 2.19)	No significant difference *p* = 0.68 Substantial heterogeneity I^2 = 93% (*p* = 0.21)
Balvers 2017	76/150 (50.7)	78/235 (33.2)	OR 2.07 (1.36, 3.15)	
Holcomb 2011	30/216 (13.9)	67/216 (31.0)	OR 0.36 (0.22, 0.58)	
Holcomb 2015	43/338 (12.7)	58/342 (17.0)	OR 0.71 (0.47, 1.09)	
Mortality, 28/30 days 3 studies, N = 1181	143/591 (24.2)	193/590 (32.7)	OR 0.58 (0.35, 0.98)	*Favours high ratio* *p* = 0.04 Moderate heterogeneity I^2 = 64% (*p* = 0.06)
Holcomb 2011	65/216 (30.1)	93/216 (43.1)	OR 0.57 (0.38, 0.85)	
Holcomb 2015	75/338 (22.2)	89/342 (26.0)	OR 0.81 (0.57, 1.15)	
Nascimento 2013	3/37 (8.1)	11/32 (34.4)	OR 0.17 (0.04, 0.67)	
High PLT:RBC ≥1 versus Low PLT:RBC 0.6 or <1				
RBC transfusion, mean 2 studies, N = 749			MD -0.73 (-1.73, 0.28)	No significant difference *p* = 0.16 No significant heterogeneity I^2 = 0% (*p* = 0.60)
Holcomb 2015	9.7 (7.4)	10.3 (7.4)	MD -0.60 (-1.71, 0.51)	
Nascimento 2013	7.7 (3.1)	9 (6.2)	MD -1.30 (-3.67, 1.07)	
Plasma transfusion, mean 2 studies, N = 749			MD 1.73 (0.87, 2.60)	*Favours high ratio* *p* <0.0001 No significant heterogeneity I^2 = 0% (*p* = 0.32)
Holcomb 2015	7.7 (7.4)	5.7 (6)	MD 2.00 (0.99, 3.01)	
Nascimento 2013	6 (3.1)	5 (3.9)	MD 1.00 (-0.68, 2.68)	

STUDY DETAILS: Rijnhout 2021
EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
The evidence is directly generalisable to the Australian population with some caveats. Patients include both military and civilian trauma patients. While military trauma is not commonly observed in Australian population, there are various elements of military trauma (e.g., lost limb, haemorrhage, etc.) that can be translated to the Australian population.
Applicability (relevance of the evidence to the Australian health care system)
The evidence is probably applicable to the Australian healthcare context with some caveats. Locations of studies were not reported, however, given the volume of studies identified, it is probable that management could be applicable to the Australian healthcare context.
Additional comments
Authors conclusions: results imply that the optimal PLT/RBC transfusion ratio approaches 1:1. Higher ratios of PLT/RBCs are associated with lower mortality at 1 hour to 6 hours, 24 hours, and 28 days to 30 days. These results should be interpreted with caution since many source studies are prone for various types of bias. Therefore, high-quality RCTs to establish optimal PLT/RBC ratio in trauma patients requiring massive transfusion are urgently needed. *List of relevant included studies:* RCT: Holcomb 2015, Nascimento 2013 Observational: Balvers 2017, Brown 2012, Cap 2012, Holcomb 2011, Inaba 2010, Lustenberger 2011, Perkins 2011, Rowell 2011, Shaz 2010, Simms 2014

CI, confidence interval; ISS, injury severity score; MD, mean difference; OR, odds ratio; PLT, platelet; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.Randomised controlled trials

Randomised controlled trials

No additional studies identified.

Observational / cohort studies

No additional studies identified.

E4 RBC volume (Question 4)

Systematic reviews/meta-analyses

STUDY DETAILS: Patel 2014			
Citation			
Patel SV, Kidane b, Klingel M, and Parry N. Risks associated with red blood cell transfusion in the trauma population, a meta-analysis. *Injury, Int. J Care Injured*. (2014). 45: 1522–1533			
Affiliation/Source of funds			
Author affiliations: London Health Sciences Centre, London Ontario Canada *Source of Funding:* Details on funding not provided. *Conflict of interest*: The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
MA of level III studies	Level I/III (40 observational studies)	Not reported	Reported for some studies, setting include ICU, trauma centres and military centre
Intervention		**Comparator**	
RBC transfusion		No RBC transfusion	
Population characteristics			
Trauma patients not limited by trauma severity, mechanism or pattern of injury			
Length of follow-up		**Outcomes measured**	
Citations published between 1947-2012 (Embase) or 1946-2012 (Medline). Literature search was conducted on 12 May 2012.		Mortality, Acute respiratory distress syndrome (ARDS), Acute lung injury (ALI), Multiorgan failure (MOF)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. *Risk of bias of included studies:* No reference to a priori design or pre-specified methods, list of excluded studies not provided, no quantitative synthesis of publication bias. The authors stated that as all included studies were observational, cohort studies, they are at risk of selection bias and confounding. The representativeness of the cohorts was good in most studies. Transfusion data was also complete in most studies. Confounding from injury severity likely limited the strength of the association between transfusion and poor outcomes, which the authors tried to mitigate by only including studies that attempted to adjust for injury severity in the pooled analysis. As injury severity is also associated with the outcomes assessed, failure to adjust for it may introduce bias that favours the intervention. The authors also noted high heterogeneity in the pooled analyses of mortality and MOF.			
RESULTS:			

Outcome **No. trials (No. patients)**	**Intervention** **n/N (%)** **Mean ± SD**	**Comparator** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** ***p*-value (I^2)**
RBC transfusion vs no RBC transfusion (continuous variable)				
Mortality 9 studies (N = 18 009) Barbosa 2011 (n = 704) Bochicchio 2008 (n = 1172) Chaiwat 2009 (n = 14070) Mahambrey 2009 (n = 260) Murrell 2005 (n = 275) Phelan 2010 (n = 399)	NR	NR	**OR 1.07 (1.04–1.10)** (with each additional unit transferred) OR 1.05 (1.03, 1.07) OR 1.05 (1.03, 1.07) OR 1.05 (1.00, 1.10) OR 1.01 (0.97, 1.05) OR 0.83 (0.69, 0.99) OR 1.13 (1.10, 1.16) OR 1.16 (1.01, 1.24)	*Favours no RBC transfusion* $p < 0.001$ Substantial heterogeneity $p < 0.0001$ ($I^2 = 82.9\%$) *GRADE: low certainty of evidence*

STUDY DETAILS: Patel 2014				
Robinson 2005 (n = 316) Spinella 2008 (n = 708) Silverboard 2005 (n = 102)			OR 1.16 (1.09, 1.25) OR 1.08 (1.04, 1.15)	
MOF 3 studies (N = 3050) Ciesla 2005 (n = 1344) Cotton 2009 (n = 266) Johnson 2010 (n = 1440)	NR	NR	**OR 1.08 (1.02–1.14)** (with each additional unit transferred) 3.40 (2.53, 4.58) 2.90 (1.20, 6.70) 8.60 (4.20, 17.70)	*Favours no RBC transfusion* p = 0.012 Substantial heterogeneity p < 0.0001 (I^2 = 95.9%) *GRADE: low certainty of evidence*
ARDS/ALI 2 studies (N = 14 136) Chaiwat 2009 (n = 14070) Edens 2010 (n = 66)	NR	NR	**OR 1.06 (1.03–1.10)** (with each additional unit transferred) 1.06 (1.03, 1.10) 1.09 (0.74, 1.58)	*Favours no RBC transfusion* p < 0.001 No heterogeneity p = 0.886 (I^2 = 0.0%) *GRADE: low certainty of evidence*
RBC transfusion vs no RBC transfusion (dichotomous variable)				
Mortality 6 studies (N = 57 875) Croce 2005 (n = 5260) Dunne 2004 (n = 9539) Malone 2003 (n = 15534) Robinson 2005 (n = 319) Texeira 2008 (n = 25599) Weinberg 2008 (n = 1624)	NR	NR	**OR 3.15 (1.82–5.46)** 2.46 (2.00, 3.20) 4.23 (3.07, 5.84) 2.83 (1.82, 4.40) 4.75 (1.37, 16.40) 6.70 (6.10, 7.50) 0.96 (0.48, 1.94)	*Favours no RBC transfusion* p < 0.001 Substantial heterogeneity p < 0.0001 (I^2 = 94.6%) *GRADE: low certainty of evidence*
MOF 3 studies (N = 2,251) Ciesla 2005 (n = 1344) Moore 1997 (n = 513) Sauaia 1994 (n = 394)	NR	NR	**OR 4.30 (2.36, 7.85)** 3.40 (2.53, 4.58) 2.90 (1.20, 6.70) 8.60 (4.20, 17.70)	*Favours RBC transfusion (≤ 6 units)* p < 0.0001 No significant heterogeneity p = 0.053 (I^2 = 65.9%) *GRADE: low certainty of evidence*
ARDS/ALI 3 studies (N = 9,230) Plurad 2007 (n = 2346) Weinberg 2008 (n = 1624) Croce 2005 (n = 5260)	NR	NR	**OR 2.04 (1.47, 2.83)** 1.98 (1.38, 2.83) 1.96 (0.73, 5.26) 3.42 (2.02, 34.20)	*Favours no RBC transfusion* p < 0.001 No heterogeneity p = 0.761 (I^2 = 0.0%) *GRADE: low certainty of evidence*
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The review included studies reporting on trauma patients with no limits placed by trauma severity, mechanism of injury or pattern of injury. This population is broader than the Guideline's target population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The location of the included studies is not stated and therefore it is unclear whether the individual studies were conducted in health care systems similar to the Australian health care system.				
Additional comments				
Authors conclusions:				

STUDY DETAILS: Patel 2014
The authors have found an association between RBC transfusion and the primary (mortality) and secondary (MOF and ARDS/ALI) outcomes, based on observational studies with high heterogeneity. *List of relevant included studies:* Balogh 2003, Balogh 2003, Barbosa 2011, Bochicchio 2008, Chaiwat 2009, Charles 2007, Ciesla 2005, Cotton 2009, Croce 2005, Cryer 1999, Dewar 2009, Dunne 2004, Dunne 2006, Earley 2006, Eberhard 2000, Edens 2010, George 2008, Hensler 2003, Johnson 2010, Madigan 2008, Maegele 2009, Mahambrey 2009, Malone 2003, Miller 2002, Mitra 2007, Moore 1997, Mostafa 2004, Murrell 2005, Phelan 2010, Plurad 2007, Plurad 2008, Robinson 2005, Sakano 1994, Sauaia 1994, Sauaia 1998, Silverboard 2005, Spinella 2008, Texeira 2008, Weinberg 2008, Weinberg 2010

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; MOF, multiorgan failure; NR, not reported; OR, odds ratio; RBC, red blood cell; SD, standard deviation

STUDY DETAILS: Balvers 2015			
Citation			
Balvers K, Wirtz MR, van Dieren S, Goslings JC & Juffermans NP. Risk factors for trauma-induced coagulopathy- and transfusion-associated multiple organ failure in severely injured trauma patients. *Frontiers in Medicine*, 2015; 2(article 24):1–11			
Affiliation/Source of funds			
Author affiliations: KB, MRW & JCG affiliated with Trauma Unit, Department of Surgery, Academic Medical Center, Amsterdam, Netherlands. KB, MRW & NPJ affiliated with Department of Intensive Care, Academic Medical Center, Amsterdam, Netherlands. SVD affiliated with Clinical Research Unit, Academic Medical Center, Amsterdam, Netherlands. *Source of funding:* None reported *Conflict of interest*: The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of 46 observational cohort studies and 4 RCTs.	I (II and III studies)	Europe, USA, Asia, Canada, Africa, Worldwide	Not reported
Intervention		**Comparator**	
Transfusion strategies (administration of fluids and RBCs)		Placebo	
Population characteristics			
Trauma patients aged ≥16 years who suffered blunt or penetrating trauma, with mean injury severity score (ISS) ≥16. Studies focused on patients with isolated traumatic brain injury (TBI) or burn injury were excluded. All included studies, except Sigurddson *et al* (1992) which included critically ill patients, included trauma patients.			
Length of follow-up		**Outcomes measured**	
Databases searched – PubMed and Embase from 1986 to 2013. In addition, ongoing trials were searched on www.controlled-trials.com and www.clinical trials.gov		Risk factors for trauma-induced coagulopathy (TIC) Transfusion-associated multiple organ failure (MOF)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The authors note that the included studies have a considerable risk of bias related to Study design and methodology and several studies did not adjust for confounders. No reference to a priori design or pre-specified methods, list of excluded studies not provided, no quantitative synthesis of publication bias. No adjustments for confounders or assessment of the impact of risk of bias on results of the review. Sources of heterogeneity not explored.			

STUDY DETAILS: Balvers 2015				
RESULTS:				
Outcome **No. trials (No. patients)**	**Intervention** **n/N (%)** **Mean ± SD**	**Comparator** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** ***p*-value (I^2)**
TIC vs non-TIC				
Development of MOF 5 observational studies (N = 12 306)	NA	NA	NA	Pooled analysis not reported due to substantial heterogeneity
Brown 2012	170/439 (38.7)	398/1438 (27.7)	RR 1.40 (1.21, 1.62)	Substantial heterogeneity (I^2 = 90%)
Cole 2013	17/42 (40.5)	25/116 (21.6)	RR 1.88 (1.13, 3.11)	
Kutcher 2012	11/24 (45.8)	15/108 (13.9)	RR 3.30 (1.74, 6.26)	
Maegele 2007	867/2989 (29.0)	688/5735 (12.0)	RR 2.42 (2.21, 2.65)	
Nydam 2011	82/192 (42.7)	196/988 (19.8)	RR 2.15 (1.75, 2.65)	
High FFP:RBC ratio ≥1:1 vs FFP:RBC <1:1				
Development of MOF 5 observational studies (N = 5431)	744/1607 (46.3)	889/1960 (45.4)	RR 1.11 (1.04, 1.19)	*Significant association* *p* = 0.003 No significant heterogeneity *p* = 0.12 (I^2 = 45%)
Borgman 2011	236/422 (55.9)	118/237 (49.8)	1.12 (0.96, 1.31)	
Holcomb 2008	12/252 (4.8)	9/166 (5.4)	0.88 (0.38, 2.04)	
Maegele 2008	133/229 (44.5)	220/484 (45.5)	1.28 (1.10, 1.48)	
Sperry 2008	65/102 (63.7)	169/313 (54)	1.18 (0.99, 1.41)	*GRADE: low certainty of evidence*
Wafaisade 2011	298/602 (49.5)	373/760 (49.1)	1.01 (0.90, 1.12)	
rVII vs placebo				
Development of MOF 2 RCTs (N = 874)	115/331 (34.7)	154/354 (43.5)	RR 0.81 (0.68, 0.98)	*Favours placebo* *p* = 0.03
Boffard 2009	7/69 (10.1)	16/74 (21.6)	0.47 (0.21, 1.07)	No significant heterogeneity *p* = 0.18 (I^2 = 44%)
Hauser 2010	108/262 (41.2)	138/280 (49.3)	0.84 (0.69, 1.01)	
Storage of RBCs				
Age of RBCs risk of MOF 1 study (N = 63)	>14 days >21 days	≤14 days ≤21 days	OR 1.16 (1.02, 1.32) OR 1.22 (1.06, 1.41)	*Significant association* *p* = 0.03 *Significant association* *p* = 0.006
Zallen 1999				
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. The study population in this review included patients who suffered blunt or penetrating trauma, with a mean ISS of ≥16. Patients with TBI and burn injury were excluded. This is a narrower patient population but is included in the Guideline's target population with consistent definitions for blunt and penetrating trauma.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. The review included studies conducted in a variety of countries including: Europe (Cole, 2013; Maegele, 2007; Borgman, 2011; Maegele, 2008; Wafaisade, 2011), USA (Brown, 2012; Kutcher, 2012; Nydam, 2011; Holcomb, 2008; Sperry, 2008), Asia, Japan, Canada, Global (Hauser, 2010), Africa (Boffard, 2009). Studies conducted in Europe may include countries with a similar healthcare system as Australia.				
Additional comments				
Authors conclusion:				

STUDY DETAILS: Balvers 2015
Early hypocoagulopathy and shock are risk factors for TIC-associated MOF in severely injured trauma patients. Later in the course of trauma, a hyper-coagulable state with the occurrence of thromboembolic events predisposes to MOF. Risk factors for transfusion-associated MOF include the administration of crystalloids and red blood cells and a prolonged storage time of red blood cells.
List of relevant included studies:
Boffard 2009, Borgman 2011, Brown 2012, Cole 2013, Hauser 2010, Holcomb 2008, Kutcher 2012, Maegele 2007, Maegele 2008, Nydam 2011, Sperry 2008, Wafaisade 2011, Zallen 1999

CI, confidence interval; FFP, fresh frozen plasma; ISS, injury severity score; ITT, intention-to-treat; MD, mean difference; MOF, multiorgan failure; NA, not available; OR, odds ratio; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; rVII, recombinant factor VII; SD, standard deviation; TIC, trauma-induced coagulopathy; USA, United States of America

Prospective cohort studies

STUDY DETAILS: Liu 2018			
Citation			
Liu S, Fujii Q, Serio F & McCague. Massive blood transfusions and outcomes in trauma patients: an intention to treat analysis. Bulletin of Emergency and Trauma. 2018; 6(3): 217-220			
Affiliation/Source of funds			
Funding sources: Details on funding not provided. *Author affiliations:* SL and AM affiliated with Natividad Medical Center, Salinas, California US. QF and FS affiliated with Touro University California, Vallego, California US. *Conflict of interest*: The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Prospective cohort	III-2	California, US	Trauma, single centre
Intervention		**Comparator**	
Higher units of PRBCs (>10 units)		Lower units of PRBCs (0-9 units)	
Population characteristics			
Patients ≥18 years with available blood transfusion information. Included patients were victims of various types of traumas who received between 0 and 87 units of PRBCs in the initial 24hrs. Patients were between the ages of 18 and 89 years; made up of 32% female and 68% male.			
Length of follow-up		**Outcomes measured**	
Patients admitted to Natividad Medical Center's trauma service from July 1,2014 to July 1 2017		Mortality Overall LOS	
Method of analysis			
All data was compiled and analysed using a Microsoft Excel database. All graphs and tables were made using either Microsoft Excel or IBM SPSS. Mortality was calculated as a percentage for each group and odds ratios were calculated by generating an outcome frequency table. Mean ISS and hospital LOS were calculated, and Student's T-tests were performed to obtain *p*-values			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has some important problems and cannot be considered comparable to a well-performed randomised trial. The sample size was reasonable (N = 131). The authors calculated mortality as a percentage and ORs were calculated by generating an outcome frequency table. Student's t-test were performed to obtain *p*-values for mean LOS.			
RESULTS			
Population analysed	**Intervention**	**Comparator**	
Available	36	95	
Analysed	36	95	
Outcome	**Intervention n/N (%) Mean ± SD**	**Comparator n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
[intervention] vs [comparator]				
Mortality 0-9 units (n = 95) 10-19 units (n = 19) 20-29 units (n = 8) 30-39 units (n = 4) 40+ units (n = 5)	 4/19 (21) 3/8 (38) 2/4 (50) 4/5 (80)	 23/95 (24)	 OR 0.83 (0.25, 2.77) OR 1.88 (0.42, 8.47) OR 3.13 (0.41, 23.49) OR 12.52 (1.33, 117.7)	OR for 40+ units was 12.52 and did not contain the null, indicating a statistically significant difference from control (0-9 units)
Overall LOS 0-9 units (n = 95)	 	 10.1 ± 12.1	 	No significant difference *p* = 0.793

STUDY DETAILS: Liu 2018				
10-19 units (n = 19) 20-29 units (n = 8) 30-39 units (n = 4) 40+ units (n = 5)	9.3 ± 5.5 9.0 ± 8.0 6.8 ± 6.0 4.6 ± 6.2			*p* = 0.806 *p* = 0.588 *p* = 0.321
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population but could be sensibly applied				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: Although this study is limited by its sample size, results suggest that 40 units of PRBCs may be a threshold at which survival rates begin to decrease significantly.				

CI, confidence interval; ISS, injury severity score; LOS, length of stay; OR, odds ratio; PRBC, packed red blood cell; SD, standard deviation; US, United States

Retrospective cohort studies

STUDY DETAILS: Hassanien 2015			
Citation			
Hassanien, M., El-Talkawy, M. D., El-Ghannam, M., El Ray, A., Ali, A. A., & Taleb, H. A. (2015). Predictors of In-Hospital Mortality in patients with hepatocellular carcinoma and Acute Variceal bleeding. *Electronic Physician*, 7(6), 1336–1343. doi:10.14661/1336			
Affiliation/Source of funds			
Source of Funding: The study was supported by Theodor Bilharz Research Institute. *Author affiliations:* Hepatogastroenterology department, Department of Environment Research, Theodor Bilharz Research Institute, Giza, Egypt (M.H., M.E-T., M.E-G., A.E.R. & A.A.A), Biostatistics and Demography, Medical Statistician, Department of Environment Research, Theodor Bilharz Research Institute, Giza, Egypt (H.A.T). *Conflict of interest*: The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort	III-3	Giza, Egypt	Single centre - Theodor Bilharz Research Institute
Intervention		**Comparator**	
Varying volume of transfusion of packed red blood cells (PRBCs)		not applicable	
Population characteristics			
Patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding			
Length of follow-up		**Outcomes measured**	
Retrospective study of eligible patients from 1 November 2013 to 31 December 2014		In-hospital mortality Complications	
Method of analysis			
All the data of the patients were registered as mean ± SE. Comparisons between groups were made using Fisher's exact and the chi squared tests for categorical variables and the Mann-Whitney tests for continuous variables. Two-sided *p*-value less than 0.05 were considered statistically significant. Multivariate models were adjusted for age, gender, diagnosis, blood units, MELD score, and serum sodium at registration. The ability of the scoring systems to discriminate between hospital survivors and non survivors was assessed by using the area under the receiver operating characteristic (AUROC) curve.			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Moderate *Description:* The study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial. The authors performed logistic regression analysis to identify independent predictors of in-hospital mortality. The sample size is small (N = 70).			
RESULTS			
Population analysed	**Intervention (Survivors)**		**Comparator (Non-survivors)**
Available	32		38
Analysed	32		38
Outcome	**Intervention n/N (%) Mean ± SE**	**Comparator n/N (%) Mean ± SE**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
Survivor vs non-survivor				
Unit of PRBCs transferred	1.9 ± 0.23	2.60 ± 0.74	NR	$p < 0.01$
Logistic regression analysis of independent predictors of mortality Bags of PRBC	NR	NR	 OR 1.38 (1.034, 1.452) OR 1.67 (1.124, 1.234)	 $p < 0.01$ $p < 0.01$

STUDY DETAILS: Hassanien 2015				
Oesophageal Varices Grade				
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The study included patients with liver cirrhosis and hepatocellular carcinoma with acute upper gastrointestinal bleeding, which may constitute a very small proportion of the Guidelines target population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. The study was conducted in a single hospital in Egypt.				
Additional comments				
Authors conclusions: The number of units of packed red blood cell transfused, MELD score at cut-off value > 12.9, high grade of Esophageal Varices and active bleeding on index endoscopy, associated major comorbidity were highly predictive of in-hospital mortality.				

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; MELD, Model for End-Stage Liver Disease; not applicable, not applicable; NR, not reported; OR, odds ratio; PRBC, packed red blood cell; SE, standard error

E5 Recombinant activated factor VII (Question 5)

Systematic reviews/meta-analyses

STUDY DETAILS: Cannon 2017			
Citation			
Cannon, J.W., Khan, M.A., Raja, A.S., Cohen, M.J., Como, J.J., Cotton, B.A., Dubose, J.J., Fox, E.E., Inaba, K., Rodriguez, C.J. and Holcomb, J.B., 2017. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. *Journal of Trauma and Acute Care Surgery,* 82(3), pp.605-617.			
Affiliation/Source of funds			
The authors declared no conflicts of interest. Author BA Cotton is a consultant, Haemonetics Corporation. Remaining authors have no affiliations to disclose. Source of funding not disclosed.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs and cohort studies (prospective and retrospective)	I /III	Not specified	Trauma
Intervention		**Comparator**	
PICO 1: MT/DCR PICO 2: High ratio of FFP and PLT to RBCs PICO 3: rFVIIa PICO 4: TXA Data for rFVIIa detailed below. Data for other interventions extracted elsewhere (Q2, Q3, Q7).		PICO 1: No MT/DCR PICO 2: Low ratio of FFP and PLT to RBCs PICO 3: No rFVIIa PICO 4: No TXA	
Population characteristics			
Patients with severe trauma at risk of death from haemorrhage, defined as patients requiring blood transfusions and/or injury severity score greater than 25. PICO 3: 2 RCTs (Hauser 2010, Boffard 2005), 3 retrospective cohorts (Harrison 2005, Rizoli 2006, Spinella 2008)			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, Medline, Embase Search dates: Jan 1985 through December 2015		Mortality (in hospital, 28 day or 30 day), Blood products used (RBC in 24, 48, or 72 hours), Massive transfusion, Morbidity (venous thromboembolic events including deep vein thrombosis or pulmonary embolism)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The authors did not provide a full list of excluded studies or details relating to risk of bias assessments, but GRADE profiles were presented. Information regarding individual studies were limited.			
RESULTS:			
Outcome **No. trials (No. patients)**	**rVIIa** **n/N (%)** **Mean ± SD (n)**	**No rVIIa** **n/N (%)** **Mean ± SD (n)**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
rVIIa versus no rVIIa				
Mortality, in-hospital, 28 or 30 days N = 1292 (2 RCTs, 3 Coh)	**112/517 (21.7%)**	**237/775 (30.6%)**	**OR 0.88 (0.64, 1.20)**	No significant difference *p* = 0.42

STUDY DETAILS: Cannon 2017				
N = 825 (2 RCTs) Boffard 2005 Hauser 2010 N = 467 (3 Coh) Harrison 2005 Rizoli 2006 Spinella 2008	66/401 (16.5%) 34/139 (24.5%) 32/262 (12.2%) 46/116 (39.7%) 12/29 (41.4%) 19/38 (50%) 15/49 (30.6%)	71/424 (16.7%) 40/144 (27.8%) 31/280 (11.1%) 166/351 (33.0%) 29/72 (40.3%) 99/204 (48.5%) 38/75 (50.7%)	OR 0.97 (0.67, 1.41) OR 0.84 (0.49, 1.43) OR 1.12 (0.66, 1.89) OR 0.78 (0.43,1.14) OR 1.05 (0.44, 2.51) OR 1.06 (0.53, 2.12) OR 0.43 (0.20, 0.92)	No significant heterogeneity I^2 = 15% (p = 0.32) No significant difference p = 0.88 No heterogeneity I^2 = 0% (p = 0.46) No significant difference p = 0.41 Moderate heterogeneity I^2 = 44% (p = 0.17)
Transfusion volume, RBC[b] N = 933 (2 RCTs, 2 Coh) N = 742 (2 RCTs) Boffard 2005 (blunt) Boffard 2005 (penetrating) Hauser 2010 (blunt) Hauser 2010 (penetrating) N = 191 (2 Coh) Harrison 2005 Spinella 2008	(n = 424) (354) 7.8 ± 12 (64) 4 ± 9.25 (69) 6.9 ± 10.4 (184) 4.5 ± 7.3 (37) (70) 29 (18.3 ± 7.5) 41 (16± 10.39)	(n = 509) (388) 7.2 ± 8.75 (72) 4.8 ± 10.25 (61) 8.1 ± 10.9 (222) 6.2 ± 6.5 (33) (121) 72 (22 ± 9) 49 (14 ±5.93)	**MD –0 .92 (–2.31, 0.47)** MD –0.94 (–2.36, 0.48) MD 0.60 (–2.97, 4.17) MD –0.80 (–4.17, 2.57) MD –1.20 (–3.28, 0.88) MD –1.70 (–4.93, 1.53) MD –0.88 (–6.46, 4.71) MD –3.70 (–7.13, -0.27) MD 2.00 (–1.59, 5.59)	No significant difference p = 0.19 No sign. heterogeneity I^2 = 17% (p = 0.30) No significant difference p = 0.20 No heterogeneity I^2 = 0% (p = 0.80) No significant difference p = 0.76 Substantial heterogeneity I^2 = 80% (p = 0.02)
Need for massive transfusion* N = 742 (3 RCTs) Boffard 2005a&b Hauser 2010	137/371 (36.9) 12/114 (10.5) 125/257 (48.6)	185/402 30/115 (26) 155/287 (54)	OR 0.68 (0.50, 0.92) OR 0.33 (0.13, 0.69) OR 0.81 (0.58, 1.13)	*Favours rFVIIa* p = 0.01 Substantial heterogeneity I^2 = 79% (p = 0.03)
Venous thromboembolic events N = 1061 (2 RCTs, 2 Coh) N = 837 (3 RCTs) Boffard 2005a&b Hauser 2010 N = 224 (2 Coh) Harrison 2005 Spinella 2008	48/487 (9.9%) 44/409 (10.8%) 6/139 (4.3%) 38/270 (14.1%) 4/78 2/29 (6.9%) 2/49 (4.1%)	57/574 (9.9%) 43/428 (10.0%) 6/138 (4.3%) 37/290 (12.8%) 14/146 14/71 (19.7%) 0/75 (0%)	OR 0.97 (0.49, 1.92) OR 1.10 (0.70, 1.72) OR 0.99 (0.31, 3.16) OR 1.12 (0.69, 1.82) OR 1.18 (0.05, 28.14) OR 0.30 (0.06, 1.42) OR 9.75 (0.37, 169.16)	No significant difference p = 0.94 Mild heterogeneity I^2 = 29% (p = 0.24) No significant difference p = 0.68 No heterogeneity I^2 = 0% (p = 0.85) No significant difference p = 0.92 Substantial heterogeneity I^2 = 72% (p = 0.06)
Retrieved from primary study				
Acute respiratory distress	3/75 (4)	1/49 (2)	RR 1.96 (0.21, 18.31)[c]	No significant difference

STUDY DETAILS: Cannon 2017				
Spinella 2008				*p* = 1.00
Multiple organ failure Spinella 2008	4/75 (5)	1/49 (2)	RR 2.61 (0.30, 22.70)c	No significant difference *p* = 0.65
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is generalisable to the Australian population with some caveats Spinella 2008 is conducted in combat patients and may not closely reflect target population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is applicable to the Australian healthcare context Spinella 2008 is conducted in combat-related injuries and may not be directly applicable. Other studies were conducted at hospitals in countries including Australia, Canada, Germany and the United States and are therefore relevant to the Australian health care system.				
Additional comments				
Results were homogenous for all outcomes except for morbidity where the RCTs and retrospective studies had conflicting results *Authors conclusions:* For most bleeding trauma patients there does not seem to be clear significant mortality benefits from rFVIIa. If given early it may decrease the need for massive transfusion. The evidence for VTEs is limited. Experts were divided on Weak recommendation (36%) vs recommend against rFVIIa or data not sufficient to recommend either way (45%) . *List of relevant included studies:* RCTs: Boffard 2005, Hauser 2010 Retrospective cohorts: Harrison 2005, Rizoli 2006, Spinella 2008				

CI, confidence interval; DCR; damage control resuscitation; FFP, fresh frozen plasma; ITT, intention-to-treat; MD, mean difference; MT, massive transfusion' OR, odds ratio; PLT, platelets; RBCs, red blood cells; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Total units in 24, 48, or 72 hours

c. Calculated post-hoc using RevMan 5.3. M-H Random effects.

STUDY DETAILS: McQuilten 2015			
Citation			
McQuilten, Z. K., Crighton, G., Engelbrecht, S., Gotmaker, R., Brunskill, S. J., Murphy, M. F., & Wood, E. M. (2015). Transfusion interventions in critical bleeding requiring massive transfusion: A systematic review. *Transfusion Medicine Reviews,* 29(2), 127-137. doi:http://dx.doi.org/10.1016/j.tmrv.2015.01.001			
Affiliation/Source of funds			
The study was funded by Australian NHMRC Centre of Research Excellence for Patient Blood Management in Critical Illness and Trauma (APP1049071). *Author affiliations:* Monash University *Conflicts of interest:* ZM and EW are employed by Monash University, whose Transfusion Research Unit has received financial support from Alexion, Amgen, Bayer, Celgene, CSL Behring, Janssen-Cilag, Takeda, Novartis, Australian Red Cross Blood Service, New Zealand Blood Service, Department of Health Victoria (Australia), NBA (Australia) and Myeloma Foundation of Australia. None of these funding sources had any involvement the design or conduct of this review.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis SRs and RCTs	I	Australia Included studies: Not reported	Any clinical setting *Dutton 2011:* 150 hospitals, non-military trauma *Houser 2010:* 150 hospitals, non-military trauma *Boffard 2005:* 32 hospitals, non-military trauma

STUDY DETAILS: McQuilten 2015	
Interventions	**Comparator**
1. RBC transfusion 2. FFP, CRYO, fibrinogen concentrate, prothrombin complex concentrate, platelet 3. rFVIIa (iv 200 g/kg at 0 hours, 100 g/kg at 1 and 3 hrs) Data for rFVIIa detailed below. Data for other interventions extracted elsewhere.	Standard of care with placebo
Population characteristics	
Patients who had critical bleeding or were anticipated to receive a massive transfusion in any clinical setting. ***RCTs*** *Dutton 2011*: Blunt and/or penetrating trauma patients; aged 18 to 70 years with continuing torso and/or proximal lower extremity bleeding after receiving 4 units RBC despite standard haemostatic interventions. *Houser 2010:* Blunt and/or penetrating trauma patients; 18 to 70 years with continuing torso and/or proximal lower extremity bleeding after receiving 4 units RBC despite standard haemostatic interventions. *Boffard 2005:* Blunt and/or penetrating trauma, aged ≥16 – <65 years who received 6 RBC units within 4 hours. ***SRs*** Simpson 2012*: Bleeding patients without haemophilia* Marti-Caravajal 2012*:* liver disease and upper gastrointestinal bleeding *Levi 2010:* off-label indications bleeding patients (and healthy volunteers)	
Length of follow-up	**Outcomes measured**
Databases: EMBASE, CINHAL, MEDLINE, Cochrane library, Transfusion Medicine evidence library **Search dates: Citations published between May 2009 and Nov 2012, with updated search conducted through to July 2014**	Mortality, Length of stay, Serious adverse events, Transfusion related adverse events, Morbidity, Transfusion rate
INTERNAL VALIDITY	
Overall risk of bias (descriptive)	
Rating (AMSTAR): Moderate *Description:* The review *may* provide an accurate summary of the results of the available studies that were included in the review. The study did not search the grey literature, provide a list of excluded studies, and did not assess publication bias. These are not considered critical flaws. *Risk of bias of included studies:* The overall risk of bias for included studies was judged by the review authors to be low to moderate. All studies were sponsored by industry support or sponsorship. The authors stated that the RCTs included had good methodological designs in all facets of assessment. With regards to the SRs, included SRs were of high quality, and included quality assessment.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**rFVIIa** **n/N (%)** **Mean ± SD**	**Placebo** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Bleeding patients (any)				
Mortality, not specified N = 2856 (1 SR, k=13 RCTs) Simpson 2012 (treatment of bleeding patients)	NR	NR	RR 0.91 (0.78, 1.06)	NR
Transfusion volume, mL RBC N = 911 (1 SR) Simpson 2012 (treatment of bleeding patients)	NR	NR	MD –89 (–264, 87)	NR
Thromboembolic adverse events	NR	NR	OR 1.17 (0.94, 1.47)	*No significant difference* *p* = 0.16

STUDY DETAILS: McQuilten 2015				
N = 4119 (1 SR, k=35 studies) Levi 2010 (off label use in bleeding patients) Arterial Venous Coronary Cerebrovascular			 OR 1.68 (1.2, 2.36) OR 0.93 (0.70, 1.23) OR 2.39 (1.39, 4.09) OR 1.27 (0.74, 2.17)	 *p* = 0.003 *p* = 0.61 *p* = 0.002 *p* = 0.39
Trauma setting				
Mortality, 30 day N = 573 (1 RCT) Hauser 2010 Penetrating and blunt Blunt trauma only	 NR/267 (18%) NR/221 (11%)	 NR/287 (13%) NR/247 (11%)	 NR NR	*No significant difference* *p* = 0.40 *p* = 0.94
Transfusion volume, RBC units to 24 hrs N = 573 (1 RCT) Hauser 2010 Penetrating and blunt Blunt trauma only *Subgroup: patients requiring massive transfusion* Penetrating and blunt Blunt trauma only N = 277 (1 RCT) Boffard 2005 Blunt Penetrating	 4.5 ± 7.3 (n=267) 6.9 ± 10.4 (n=221) 14 ± 30.4 (n=NR) 111 ± 50.2 (n=NR) NR (n=69) NR (n=70)	 6.2 ± 6.5 (n=287) 8.1 ± 10.9 (n=247) 21 ± 52.5 (n=NR) 134 ± 54.3 (n=NR) NR (n=74) NR (n=64)	 NR NR NR NR estimated reduction[b] 2.0 (0.0, 4.6) 0.2 (–0.9, 2.4)	 No significant difference *p* = 0.11 *Favours rFVIIa* *p* = 0.04 *Favours rFVIIa* *p* = 0.04 No significant difference *p* = 0.38 No significant difference *p* = 0.07 *p* = 0.24
Transfusion volume, allogenic units to 24 hrs N = 573 (1 RCT) Hauser 2010 Penetrating and blunt Blunt trauma only	 11.2 ± 15 (n=267) 17.1 ± 26.8 (n=221)	 16.8 ± 19.3 (n=287) 20.7 ± 25.7 (n=247)	 NR NR	No significant difference *p* = 0.09 *Favours rFVIIa* *p* = 0.03
Thromboembolic events N = 560 (1 RCT) Dutton 2011 Venous Arterial	 25/270 (9) 16/270 (6)	 26/287 (9) 12/290 (4)	 NR NR	 No significant difference *p* = 0.90 *p* = 0.33
Multiorgan failure, 30 day N = 573 (1 RCT) Hauser 2010 Penetrating and blunt Blunt trauma only	 NR/267 (23) NR/221 (45)	 NR/287 (24) NR/247 (53)	 NR NR	 No significant difference *p* = 0.09 *p* = 0.06
ARDS N = 560 (1 RCT) Dutton 2011	8/270 (3)	21/290 (7.2)	NR	*Favours intervention* *p* = 0.02
All adverse events N = 560 (1 RCT)	240/270 (89)	256/290 (88)	NR	No significant difference *p* = 0.82

STUDY DETAILS: McQuilten 2015				
Dutton 2011				
Serious adverse events N = 560 (1 RCT) Dutton 2011	165/270 (61)	197/290 (68)	NR	No significant difference *p* = 0.09
Medical setting (GI bleeding)				
Mortality, 5 days N = 510 (1 SR, k=2 RCTs) Marti-Caravajal 2012	NR	NR	RR 0.95 (0.36, 2.50)	No significant difference *p* = 0.16
Mortality, 42 days N = 510 (1 SR, k=2 RCTs) Marti-Caravajal 2012	NR	NR	RR 1.01 (0.55, 1.87)	No significant difference *p* = 0.14
Thromboembolic adverse events N = 510 (1 SR, k=2 RCTs) Marti-Caravajal 2012	NR	NR	RR 0.80 (0.40, 1.6)	No significant difference *p* = 0.20
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats				
Additional comments				
Authors conclusions: The available evidence confirms that the off-label use of rFVIIa in critical bleeding or trauma confers no benefit to mortality outcomes. In the SR by Simpson et al, there was a modest reduction in red cell transfusion requirements and blood loss; however, this effect may have been overestimated as some of the negatively weighted studies were not able to be incorporated into the meta-analysis. This possible benefit was offset by a trend toward an increased risk of thromboembolic events, and a significantly increased risk of arterial thromboembolic events when both prophylactic and therapeutic studies were considered. At present, the evidence does not support the routine use of rFVIIa as part of the treatment algorithm in the management of critical bleeding or as part of an MTP. *List of relevant included studies* 3 RCTs: Dutton 2011, Hauser 2010, Boffard 2005 3 SRs: Simpson 2012; Marti-Caravajal 2012; Levi 2010				
CB, critical bleeding; CI, confidence interval; d, day; hrs, hours; MD, mean difference; MT, massive transfusion; MTP, massive transfusion protocol; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SR, systematic review a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%. b. Hodges-Lehmann point estimate of the shift in transfusion amount from placebo to active group, including 90% CI. Patients who died within 48 hours were assigned the highest rank (see Boffard 2009).				

STUDY DETAILS: Magon 2012			
Citation			
Magon, N., & Babu, K. (2012). Recombinant Factor VIIa in Post-partum Hemorrhage: A New Weapon in Obstetrician's Armamentarium. *N Am J Med Sci,* 4(4), 157-162. doi:10.4103/1947-2714.94938			
Affiliation/Source of funds			
The authors declared the study received no funding. The authors declared they had no conflicts of interest. Department of Obstetrics and Gynaecology, Air Force Hospital, India			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic literature review and case series	I/ IV	India	Obstetrics and gynaecology

STUDY DETAILS: Magon 2012	
Intervention	**Comparator**
rFVIIa	Not stated
Population characteristics	
Women with post-partum haemorrhage (intractable bleeding with no other obvious indications for hysterectomy)	
Length of follow-up/Search details	**Outcomes measured**
Databases searched: Medline Search date: Not provided	No outcomes reported
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. No studies were included. Literature search details, study selection criteria, or list of excluded studies not provided. *Risk of bias of included studies:*	

RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Therapeutic rFVIIa versus no rFVIIa				
No studies found				
Generalisability (relevance of the study population to the Guidelines target population)				
No evidence presented in this SR				
Applicability (relevance of the evidence to the Australian health care system)				
No evidence presented in this SR.				
Additional comments				
A case series of three patients was reported. The authors recommend rFVIIa be made available and considered early for cases of intractable PPH prior to hysterectomy. They suggest Hg should be above 7g/dL, INR <1.5, platelets above 50000/cumm, fibrinogen levels at minimum 100 mg/dL but preferably > 150 mg/dL, pH ≥ 7.2, and body temperature within physiological values.				

CI, confidence interval; Hg, haemoglobin; INR, international normalised ratio; rFVIIa, activated recombinant factor seven; SD, standard deviation

STUDY DETAILS: Okanta 2012			
Citation			
Okanta, K.E., Edwin, F. & Falas, B. 2012. Is recombinant factor VII effective in the treatment of excessive bleeding after paediatric cardiac surgery? Interactive Cardiovascular and Thoracic Surgery, 15, 690-695.			
Affiliation/Source of funds			
The authors declared they had no conflicts of interest. Affiliation: Division of Cardiothoracic Surgery, Department of Surgery, University College Hospital, PMB 5116, Ibadan, Nigeria. Source of funds not reported			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of best evidence No RCTs identified (see comments below)	Level I / III		Surgical
Intervention		**Comparator**	
rFVIIa to treat bleeding		No rFVIIa	

Population characteristics				
Children younger than 1 year of age, with excessive bleeding after cardiac surgery refractory to conventional methods of achieving haemostasis				
Length of follow-up		**Outcomes measured**		
Medline using the PubMed interface **Citations published between 1966 to Feb 2012.**		Chest tube drainage, plasma prothrombin time, activated partial thromboplastin time, reduction in transfusion of blood products, thrombosis, death		
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. The study did not have independent data extraction. No list of excluded studies was provided, nor referenced. The authors did not mention formal strategies to rate the quality of the assembled evidence. The authors did not mention formal strategies to rate publication bias. Authors stated no conflict of interest, but no declaration of funding. *Risk of bias of included studies:*				
RESULTS:				
Outcome **No. trials (No. patients)**	**rFVIIa** **n/N (%)** **Mean ± SD**	**No rFVIIa** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** **I^2 (p-value)**
Therapeutic rFVIIa versus no rFVIIa				
No studies met the PICO criteria				
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
NA				
Applicability (relevance of the evidence to the Australian health care system)				
NA				
Additional comments				
List of included studies (patients with critical bleeding) Ekert 2006, Warren 2009, Karsies 2010, Agarwal 2007, Kylasam 2006, Pychynka-Pokarska 2004, Tobias 2004, Guzzetta 2009, Egan 2004, Niles 2008, Veldman 2007, Singh 2012, Razon 2005				

CI, confidence interval; MA, meta-analysis; NA, not applicable; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review

STUDY DETAILS: Simpson 2012			
Citation			
Simpson, E., Lin, Y., Stanworth, S., et al. 2012. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane database of systematic reviews* (Online), 3, CD005011.			
Affiliation/Source of funds			
The authors declared potential conflicts of interest relating to involvement as study site investigator for off-label use of rFVIIa funded by Novo Nordisk (YL) and as past employee of the NHS blood and transplant service (CH). Cochrane Review funded by the National Blood Service, Research and Development, UK; Canadian Blood Services, Canada; Department of Clinical Pathology, Sunnybrook Health Sciences Centre, Canada.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic Review of RCTs	Level I	*Hauser 2010:* 26 countries *Boffard 2005:* Australia, Canada, France, Germany, Israel, Singapore, South Africa, United Kingdom	Multicentre, in-hospital trauma, surgical, medical

STUDY DETAILS: Simpson 2012			
		Bosch 2004: 26 hospitals throughout Europe *Bosch 2008:* 31 hospitals in 12 countries in Europe and Asia *Pihusch 2005:* 46 study locations in numerous countries in US, UK, Europe and Asia-Pacific *Chuansumrit 2005:* Thailand, Philippines *Narayan 2008:* Canada, Finland, Germany, India, Israel, Italy, Singapore, Spain, Switzerland, and Taiwan	
Intervention		**Comparator**	
This Cochrane review was broader than our study population and included both prophylactic and therapeutic use of rFVIIa. Only data from studies reporting therapeutic use of rFVIIa to treat bleeding were extracted. *Hauser 2010a&b*: rFVIIa iv at 0, 1, 3 hrs; total 400 µg/kg *Boffard 2005a&b*: rFVIIa iv at 0, 1, 3 hrs; total 400 µg/kg *Bosch 2004:* rFVIIa iv at 0, 2, 4, 6, 12, 18 & 24 hrs; total 700 µg/kg *Bosch 2008:* rFVIIa iv at 0, 2, 8, 14, & 20 hrs; total 1000 µg/kg *Pihusch 2005:* rFVIIa iv every 6 hrs at 40, 80 or 160 µg/kg; total 280, 560, 1120 *Chuansumrit 2005:* rFVIIa iv 100 µg/kg with repat dose at 30 minutes if ongoing bleeding *Narayan 2008:* rFVIIa iv single dose 40, 80, 120, 160 or 200 µg/kg within 2.5 hrs of CT scan		Placebo	
Population characteristics			
Patients at risk of blood loss due to surgery, or who had received treatment to manage bleeding. The authors considered all age groups but excluded patients with haemophilia or other haemostatic defects (for example, Glanzmann's thrombasthenia, inherited factor VII deficiency). Study population of this Cochrane review was broader than our study population and included patients with: stem cell transplantation, cirrhosis, complex non-coronary cardiac surgery requiring CPB, congenital heart disease, elective cardiac revascularisation requiring CPB, cardiac valve replacement requiring CPB, retropubic prostatectomy, cardiac surgery requiring CPB and admitted to a postoperative care, congenital craniofacial malformation, thermal burn undergoing skin excision and grafting, liver carcinoma/metastasis, benign tumours or anatomical/nonanatomical resection, spontaneous ICH, reconstructive surgery, spinal fusion surgery. Data from 9 RCTs conducted in patients ***with*** critical bleeding were extracted. *Hauser 2010a:* adult patients who had sustained blunt trauma and had received minimum 4U RBCs but not completed 8U within 12 hours of injury *Hauser 2010b:* adult patients who had sustained penetrating trauma and had received minimum 4U RBCs but not completed 8U within 12 hours of injury *Boffard 2005a:* adult patients with severe bleeding due to blunt trauma *Boffard 2005b:* adult patients with severe bleeding due to penetrating trauma *Bosch 2004:* adult patients with cirrhosis and upper gastrointestinal haemorrhage *Bosch 2008:* adult patients with cirrhosis and upper gastrointestinal haemorrhage *Pihusch 2005:* patients (aged >12 yrs.) with bleeding occurring 2 to 180 days after haematopoietic stem cell transplant *Chuansumrit 2005*: children with dengue haemorrhagic fever *Narayan 2008:* adult patients with traumatic ICH with contusion of total volume of at least 2 mL on CT scan within 6 hours of injury		

STUDY DETAILS: Simpson 2012	
Length of follow-up	**Outcomes measured**
Follow-up generally not specified, but usually period of hospitalisation	Mortality Morbidity (bleeding and thromboembolic events) Transfusion volume RBCs
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* The overall risk of bias of the included studies was mainly judged to be low to unclear. In most cases, the threats to validity were assessed as minimal or 'unclear' because details were not provided in the publications. Boffard 2005a and 2005b were judged as having a high risk of selective reporting bias, with important threats to validity, as patients who died within 48 hours were excluded from analysis and data for all patients were not available. Hauser 2010a and Hauser 2010b were considered to have an unclear risk of bias due to unclear blinding of outcome assessment, which may have favoured the intervention. Chuansumrit 2005 was considered to have a high risk of bias due to no power calculations. Narayan 2008 was judged as having an unclear risk of bias due to inclusion criteria changing after 8% of participants entered the study.	
RESULTS:	

Outcome **No. patients (No. trials)**	**rFVIIa** **n/N (%)** **Mean ± SD (n)**	**No rFVIIa** **n/N (%)** **Mean ± SD (n)**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** **I^2 (*p*-value)**
Therapeutic rFVIIa versus placebo or no rFVIIa				
Mortality N = 2856 (13 RCTs) (Includes patients with spontaneous ICH)	**332/1777**	**202/1079**	**RR 0.91 (0.78, 1.06)**	No significant difference *p* = 0.2 No significant heterogeneity I^2 = 0% (*p* = 0.66)
Mortality (patients with critical bleeding only)				
Hauser 2010a	26/224	28/250	RR 1.04 (0.63, 1.71)	
Hauser 2010b	8/46	5/40	RR 1.39 (0.49, 3.91)	
Boffard 2005a	17/69	22/74	RR 0.83 (0.48, 1.42)	
Boffard 2005b	17/70	18/64	RR 0.86 (0.49, 1.53)	
Bosch 2004	16/116	11/120	RR 1.50 (0.73, 3.10)	
Bosch 2008	39/170	25/86	RR 0.79 (0.51, 1.21)	
Pihusch 2005	24/77	7/23	RR 1.02 (0.51, 2.07)	
Chuansumrit 2005	0/16	0/9	Not estimable	
Narayan 2008	7/61	4/36	RR 1.03 (0.32, 3.29)	
Control of bleeding (number of patients with reduced bleeding) N = 616 (4 RCTs)	300/380	183/236	RR 0.95 (0.88, 1.03)	No significant difference *p* = 0.21 No significant heterogeneity I^2 = 0% (*p* = 0.57)
Bosch 2004	102/118	100/119	RR 0.97 (0.87, 108)	
Bosch 2008	142/170	66/86	RR 0.92 (0.80, 1.05)	
Pihusch 2005	44/76	13/22	RR 1.02 (0.69, 1.52)	
Chuansumrit 2005	12/16	4/9	RR 0.59 (0.27, 1.30)	

STUDY DETAILS: Simpson 2012				
Total thromboembolic events N = 2856 (13 RCTs) (includes patients with spontaneous ICH)	169/1789	89/1084	1.14 (0.89, 1.47)	No significant difference *p* = 0.30 No significant heterogeneity I^2 = 0.0% (*p* = 0.67)
Total TE events (patients with critical bleeding only)				
Hauser 2010a	36/224	33/250	1.22 (0.79, 1.88)	
Hauser 2010b	2/46	4/40	0.43 (0.08, 2.25)	
Boffard 2005a	2/69	3/74	0.71 (0.12, 4.15)	
Boffard 2005b	4/70	3/64	1.22 (0.28, 5.24)	
Bosch 2004	7/121	7/121	1.00 (0.36, 2.76)	
Bosch 2008	9/176	7/89	0.65 (0.25, 1.69)	
Pihusch 2005	8/77	0/23	5.23 (0.31, 87.34)	
Chuansumrit 2005	0/16	0/9	Not estimable	
Narayan 2008	13/61	5/36	1.53 (0.60, 3.95)	
Transfusion volume RBCs, mL [a] N = 911 (5 RCTs)	(n = 443)	(n = 468)	MD –88.60 (–263.88, 86.68)	No significant difference *p* = 0.32 Mild heterogeneity I^2 = 16% (*p* = 0.32)
Hauser 2010a	2340 ± 3180 (191)	2730 ± 3390 (228)	–390.00 (–1020.09, 240.09)	
Hauser 2010b	1500 ± 2220 (39)	2040 ± 2070 (35)	–540.00 (–1517.62, 437.62)	
Bosch 2004	450 ± 1110 (121)	390 ± 570 (121)	60.00 (–162.33, 282.33)	
Bosch 2008	764 ± 719 (76)	990 ± 930 (75)	–226.00 (–491.39, 39.39)	
Chuansumrit 2005 [b]	131 ± 812 (16)	103 ± 102 (9)	28.00 (–375.41, 431.41)	
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian health care system with few caveats The studies are conducted in multiple countries, including those with similar health care systems to Australia.				
Additional comments				
Authors conclusion: The effectiveness of rFVIIa remains unproven. The results indicate increased risk of arterial events. The use of rFVIIa beyond licensed use should remain restricted to clinical trials. There was no effect on mortality (RR 1.04; 95%CI 0.55 to 1.97). Modest benefits were found in the outcomes of blood loss and red cell transfusion requirements (less than one red cell unit saved with rFVIIa treatment); however, these favourable findings were likely overestimated because data were not available from larger negative studies for inclusion in the meta-analysis. A statistically non-significant trend towards an increased risk of thromboembolic events with rFVIIa was also observed.				
List of included studies (patients with critical bleeding) Hauser 2010, Riou 2005, Bosch 2004, Bosch 2008, Chuansumrit 2005, Pihusch 2005, *List of ongoing studies that may be relevant* Gajewski 2005, Gris 2006, Kelleher 2006, Gill 2009,McCall 2005 *List of excluded studies (patients do not meet our PICO)* Narayan 2008				

CI, confidence interval; CPB, cardio-pulmonary bypass; ICH, intracranial haemorrhage; MD, mean difference; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Simpson 2012 noted that Boffard 2005a and Boffard 2005b reported data as median volume, and therefore were not included in the meta-analysis. The exclusion of these studies was considered unlikely to alter the pooled MD as the studies found no significant difference between treatment groups for this outcome at 48 hours.

b. Simpson 2012 converted data provided as per kg to mL according to average weights for the mean age indicated.

STUDY DETAILS: Curry 2011			
Citation			
Curry, N., Hopewell, S., Doree, C., Hyde, C., Brohi, K., & Stanworth, S. (2011). The acute management of trauma hemorrhage: A systematic review of randomized controlled trials. *Critical Care,* 15 (2) (no pagination)(R92). doi:http://dx.doi.org/10.1186/cc10096			
Affiliation/Source of funds			
The study was funded by the National Institute for Health Research Programme Grant for Applied Research (R*P*-PG-0407-10036). *Author affiliations:* NHS Blood and Transplant, Systematic Review Initiative (SRI), NHS Blood and Transplant, John Radcliffe Hospital, Oxford, UK Cochrane Centre The authors declared they had no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and narrative analysis of RCTs	I	List countries of the included studies not provided	Trauma
Intervention		**Comparator**	
rFVIIa *Boffard 2005:* 400 µg/kg over 3 doses *Hauser 2010:* 400 µg/kg over 3 doses		Standard of care (placebo)	
Population characteristics			
Patients with haemorrhagic shock within the first 24 hours of injury *Boffard 2005:* Adults patients with blunt or penetrating injury, requiring > 6U RBC in 4hrs *Hauser 2010:* Adult patients with blunt or penetrating injury with ongoing bleeding after 4U RBC			
Length of follow-up		**Outcomes measured**	
Follow up of individual studies not reported Databases searched: Medline, Embase, Cochrane library (CENTRAL, CCTR, Injuries Group specialist register), ICTRP, ClinicalTIrials.gov, NHSBT SRI) **Citations published between database inception to July 2010**		Mortality Morbidity (Multiple organ failure rates, acute respiratory distress, infection) Transfusion volume (RBC, FFP)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. The review did not provide a list of excluded studies and did not assess publication bias. Reporting of outcome data was limited. *Risk of bias of included studies:* The overall risk of bias for included studies was judged by the review authors to be unclear. The reporting in the studies was insufficient to make a judgement about the quality of the included studies with no explanations given for missing data. The bias is likely to favour the intervention.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**rFVIIA** **n/N (%)** **Mean ± SD**	**placebo** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
rFVIIa versus placebo				
Mortality N = 850 (3 RCTs) Boffard 2005a (blunt) Boffard 2005b (penetrating) Hauser 2010 (blunt)	**NR/412** NR/69 NR/70 NR/226 NR/47	**NR/438** NR/74 NR/64 NR/255 NR/45	Not calculated	No significant difference *p* = 0.58 *p* = 0.69 *NR* *NR*

STUDY DETAILS: Curry 2011				
Hauser 2010 (penetrating)				
Transfusion volume, PRBC N = 850 (3 RCTs) Boffard 2005a (blunt) Boffard 2005b (penetrating) Hauser 2010 (blunt) Hauser 2010 (penetrating)	**(412)** NR (69) NR (70) NR (226) NR (46)	**(438)** NR (74) NR (64) NR (255) NR (45)	NR	*Favours rFVIIa (blunt)* *Authors reported a trend towards reduction in penetrating trauma
Multiple organ failure N = 850 (3 RCTs) Boffard 2005a (blunt) Boffard 2005b (penetrating) Hauser 2010 (blunt & penetrating)	NR/411 NR/69 NR/70 NR/272	NR/438 NR/74 NR/64 NR/300	NR	 NR (no difference) NR (trend towards) NR (trend towards in blunt injury)
Acute respiratory distress N = 850 (3 RCTs) Boffard 2005a (blunt) Boffard 2005b (penetrating) Hauser 2010 (blunt & penetrating)	NR/411 NR/69 NR/70 NR/272	NR/438 NR/74 NR/64 NR/300	NR	 NR (favours rFVIIa) NR (no difference) NR (trend towards in blunt injury)
Retrieved from primary studies				
Multiple organ failure Boffard 2005 (blunt) Boffard 2005 (penetrating) Hauser 2010 (blunt)* Hauser 2010 (penetrating)* * Denver organ failure score >3 through to day 30	 5/69 (7) 4/70 (6) 98/218 (45.0) 10/44 (22.7)	 9/74 (12) 7/64 (8) 129/242 (53.3) 9/38 (23.7)	NR	 p = 0.41 p = 0.09 p = 0.06 p = 0.90
Acute respiratory distress Boffard 2005a (blunt) Boffard 2005b (penetrating)	 3/69 (4) 4/70 (6)	 12/74 (16) 5/64 (8)	NR	 p = 0.03 p = 0.74
Subgroup analyses of Boffard 2005a&b				
Mortality N = 169 (1 RCT) McMullin 2010 (post-dose PT ≥ 18 seconds)	NR/86	NR/83	NR	*Favours PT < 18 sec at 1 hour in rFVIIa arm* $p \leq 0.001$
Massive transfusion [b] N = 169 (1 RCT) McMullin 2010 (post-dose PT ≥ 18 seconds)	NR (86)	NR (83)	NR	*Favours PT < 18 sec at 1 hour in rFVIIa arm* p = 0.02
Transfusion volume, PRBC N = 136 (1 RCT) Rizoli 2006 (coagulopathic patients)	NR (60)	NR (76)	NR	*Favours rFVIIa* p = 0.02
Transfusion volume, FFP N = 136 (1 RCT) Rizoli 2006 (coagulopathic patients)	NR (60)	NR (76)	NR	*Favours rFVIIa* p = 0.04

STUDY DETAILS: Curry 2011				
Transfusion volume, platelets N = 136 (1 RCT) Rizoli 2006 (coagulopathic patients)	NR (60)	NR (76)	NR	No significant difference *p* = 0.09
Multiple organ failure N = 277 (1 RCT) Rizoli 2006 (coagulopathic patients) Boffard 2009 (patients surviving 48 hours or more)	NR/139 NR/60 NR/69 (blunt) NR/70 (penetrating)	NR/138 NR/76 NR/74 NR/64	NR NR OR 0.05 (0.0, 0.89) NR	 NR (trend towards) NR Favours intervention (blunt)
Acute respiratory distress N = 277 (1 RCT) Rizoli 2006 (coagulopathic patients) Boffard 2009 (patients surviving 48 hours or more)	NR/60 NR/139	NR/76 NR/138	NR OR 0.16 (0.02, 0.73)	NR (favours rFVIIa) NR (favours rFVIIa)
Multiple organ failure and acute respiratory distress N = 277 (1 RCT) Boffard 2009 (patients surviving 48 hours or more)	NR/139	NR/138	OR 0.16 (0.02, 0.81)	*Favours rFVIIa* (blunt injury) NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: The multifactorial nature of trauma haemorrhage, issues with trial design and conduct, and lack of co-ordinated approach means only limited conclusions can be drawn. The available evidence does not demonstrate a correlation between survival or reduction in transfusion requirements. *List of relevant included studies:* RCTs: Boffard 2005a&b, Hauser 2010 Subgroup analysis of Boffard 2005 a&b: Rizoli 2006, Boffard 2009, McMullin 2010				

CCTR, Current controlled trials registry; CI, confidence interval; ICTRP, international clinical trials registry platform; ITT, intention-to-treat; MD, mean difference; NHSBT SRI, National Health Service blood and transplant systematic review initiative; PRBC, packed red blood cells; PT, prothrombin time; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if P_{het} >0.1 and I2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

b. Massive transfusion defined as 20 units of RBC within 48 hr of admission.

STUDY DETAILS: Yank 2011
Citation
Yank, V., Tuohy, C.V., Logan, A.C., et al. 2011. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Annals of Internal Medicine*, 154, 529-40. Comparative Effective Review no. 21. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, et al. Comparative effectiveness of recombinant factor VIIa for off-label indications versus usual care. Prepared by Stanford-UCSF Evidence-based Practice Center under contract no. 290-02-0017. Rockville, MD: Agency for Healthcare Research and Quality; 2011. The full report was reassessed in August 2016 and conclusions were considered current.

STUDY DETAILS: Yank 2011			
See https://effectivehealthcare.ahrq.gov/topics/recombinant-factor-viia/research			
Affiliation/Source of funds			
Primary funding provided by the US Agency for Healthcare Research and Quality, with additional support from the National Heart, Lung, and Blood Institute and the Palo Alto Medical Foundation Research Institute. The authors declared potential conflicts of interest relating to employment (Stanford Hospital), grants (monies to institutions), travel for meetings, consultancy (Sanofi-Aventis), and expert testimony (Mylan Pharmaceuticals). Full disclosures are available online.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of comparative studies	Level I	*Boffard 2005:* Australia, Canada, France, Germany, Israel, Singapore, South Africa, UK *Hauser 2010:* 26 countries including US *Gill 2009:* 13 countries in Africa, Asia, Europe, South America and US	In-hospital, off-label use Relevant to this report: surgical (cardiac), trauma Not relevant: ICH, liver transplant, prostatectomy
Intervention		**Comparator**	
rFVIIa Three sequential infusions of rFVIIa (200, 100 and 100 µg/kg)		Alternative therapies, placebo or usual care	
Population characteristics			
Trauma: Patients with acquired, coagulopathic massive bleeding from body trauma *Cardiac surgery:* Patients who had undergone cardiac surgery and were bleeding.			
Length of follow-up		**Outcomes measured**	
30 days from rFVIIa administration		Mortality* Thromboembolic events Transfusion volume * noted Hauser terminated early due to unexpectedly low mortality and likelihood of being underpowered to meet primary endpoint	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* study quality was assessed using nine predefined criteria. *Trauma:* Two RCTs and three Coh studies were all assessed to be of fair quality. Two poor quality Coh studies were excluded. *Cardiac surgery:* One good quality RCT (Gill 2009), one fair quality RCT, and four Coh studies (two good quality and two fair quality)			
RESULTS:			

Outcome **No. patients (No. trials)**	**rFVIIa** **n/N (%)** **Mean ± SD**	**No rFVIIa** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** **I^2 (*p*-value)**
Trauma				
Mortality, 30-days N = 277 (2 RCTs)				
Boffard 2005a (blunt)	NR/69 (24.6)	NR/74 (29.7)	NR	*p* = 0.58
Boffard 2005b (penetrating)	NR/70 (24.3)	NR/64 (28.1)	NR	*p* = 0.69
Thromboembolic events				

STUDY DETAILS: Yank 2011				
N = 277 (2 RCTs) Boffard 2005a (blunt) Boffard 2005b (penetrating)	 NR/69 (2.9) NR/70 (5.7)	 NR/74 (4.1) NR/64 (4.7)	 NR NR	 NR NR
ARDS N = 277 (2 RCTs) Boffard 2005a (blunt) Boffard 2005b (penetrating)	 NR/69 (4.3) NR/70 (5.7)	 NR/74 (16.2) NR/64 (7.8)	 NR NR	 *p* = 0.03 *p* = 0.74
RBC transfusion, units up to 48 hours N = 220 (2 RCTs) Boffard 2005a (blunt) Boffard 2005b (penetrating) * patients who died within 48 hours were excluded	 6.9 ± 6.2 (52) 4.5 ± 5.3 (57)	 10.9 ± 9.3 (59) 7.7 ± 9.9 (52)	 NR NR	 *p* = 0.02 *p* = 0.10
Cardiac surgery				
Mortality N = 172 (1 RCT) Gill 2009 40 ug/kg rFVIIa 80ug/kg rFVIIa	 10/104 4/35 (11.4) 6/69 (8.7)	 4/68 (5.8)	 RD 0.04 (–0.04, 0.12)	No significant difference Heterogeneity NA NR
Thromboembolic events N = 172 (1 RCT) Gill 2009 40 ug/kg rFVIIa 80ug/kg rFVIIa	 7/104 (6.7) 3/35 (8.6) 4/69 (5.8)	 1/68 (1.5)	 RD 0.05 (0.00, 0.11)	*Favours rFVIIa (borderline)* NR
Total transfusion volume*, mL median (IQR) N = 172 (1 RCT) Gill 2009 40 ug/kg rFVIIa 80ug/kg rFVIIa *inclusive of all products	 (n = 104) 640 (0, 1920) 500 (0, 1750)	 (n = 68) 825 (326.5, 1893)	 NR	*Favours rFVIIa* *p* = 0.047 *p* = 0.042
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats *Trauma:* Included both blunt and penetrating trauma, civilian patients. Despite differences in mechanism of injury, the physiologic characteristics are shared, and are deemed appropriate to assess together. Censoring of patients who experience early in-hospital mortality may affect generalisability. *Cardiac surgery:* Population included adult cardiac surgery patients.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats Trauma: evidence includes a variety of countries and health systems, many of which are similar to Australia. Some differences in regional centres may exist. Cardiac surgery: evidence includes countries with a health care system similar to Australia.				
Additional comments				
Authors conclusions *Trauma:* low strength evidence suggests the potential for benefit and little evidence of increased harm. Evidence is limited by lack of power for evaluating mortality. Subgroups suggest greater benefit in patients with blunt trauma, higher baseline pH, shorter time to administration, and higher platelet count.				

STUDY DETAILS: Yank 2011
Cardiac surgery: moderate strength evidence (TE) and low strength evidence (other outcomes) suggests neither benefit nor harms substantially exceed each other. Subgroups suggest greater benefit with earlier treatment. *List of included studies (patients with critical bleeding)* *Trauma:* Hauser 2010, Boffard 2005a, Boffard 2005b, Spinella 2008, Rizoli 2006; Fox 2009 *Cardiac surgery:* Gill 2009 , Diprose 2005
CI, confidence interval; ITT, intention-to-treat; mL, millilitres; RCT, randomised controlled trial; RD, risk difference; SD, standard deviation a. Data derived from figure 2 in Boffard 2005. *P*-values calculated using one-sided Wilcoxon-Mann-Whitney rank test

STUDY DETAILS: Franchini 2010			
Citation			
Franchini, M., Franchi, M., Bergamini, V., Montagnana, M., Salvagno, G. L., Targher, G., & Lippi, G. (2010). The use of recombinant activated FVII in postpartum hemorrhage. *Clinical Obstetrics and Gynecology*, 53(1), 219-227. doi:http://dx.doi.org/10.1097/GRF.0b013e3181cc4378			
Affiliation/Source of funds			
Details on funding or potential conflicts of interest not provided. University Hospital Parma, Italy			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of observational studies, case series and registries No RCTs, case-control, or interventional cohort studies identified (see comments below)	I / IV	Italy Registries from various countries including Europe and Australia	Obstetrics and gynaecology
Intervention		**Comparator**	
rFVIIa of varying doses median dose 1.5 µg/kg (range 10–137 µg/kg) number of doses 1.1 (range 1–3)		Nil	
Population characteristics			
Severe postpartum haemorrhage (≥ 500 mL after vaginal delivery and ≥ 1000 mL after caesarean delivery) Mean age 31.3 years, 121 (51.5%) vaginal delivery Reasons for worsening PPH: uterine atony (11/222, 51.3%); uterine or vaginal laceration (62/222, 27.9%); placental abnormalities (50/222, 22.5%); retained placenta (23/222, 10.4%)			
Length of follow-up		**Outcomes measured**	
Databases searched: EMBASE, Medline **Search date: Citations published between database inception and Dec 2008**		Response (defined as cessation or reduction of bleeding) Morbidity (adverse events)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. No reference to protocol or study selection criteria. The included studies are case series only and therefore no comparative data is provided. *Risk of bias of included studies:* The authors intended to use the Newcastle-Ottawa scale and the Cochrane Risk of Bias tool to assess the methodological quality of the included studies, but no comparative studies were found.			

RESULTS:				
Outcome **No. patients** **(No. trials)**	**rFVIIa** **n/N (%)** **Mean ± SD**	**no rFVIIa** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Response (cessation or significant reduction in bleeding) N = 282 (9 case series)	240/282 (85.1)	-	-	-
Hysterectomy N = 282 (9 case series)	110/225 (43.1)	-	-	-
Adverse events N = 282 (9 case series)	7/282 (2.48) 2 pulmonary embolism 4 venous thromboembolism 1 myocardial infarction	-	-	-
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats Study includes data from the Australian and New Zealand Registry (Isbistar 2008) which collects data on all use of rFVIIa at participating institutions for nonhaemophiliac patients				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats				
Additional comments				
Authors conclusions: The authors identified no RCTs, case-control, or interventional cohort studies, therefore attempted to extract useful information from published case reports (N>10) to provide recommendations for the management of severe PPH. Data from 9 studies involving 272 women were reviewed. The authors concluded that the use of rFVIIa may provide a beneficial role in the management of PPH refractory to standard treatment. The recommendations on the management of PPH with rFVIIa are: - Consider the use of rFVIIa only after the failure of medical (treatment of hemodynamic instability, hypothermia, and metabolic abnormalities; uterine massage/ compression; and uterotonic agents), blood component (transfusion of RBC, platelet, and fresh-frozen plasma to correct anaemia, thrombocytopenia, and coagulopathy), and conservative surgical/invasive (B-Lynch suture, internal iliac or uterine artery ligation, internal uterine tamponade, and uterine artery radiologic embolization) therapies. - Administer rFVIIa 90 µg/kg as an intravenous bolus over 3 to 5 minutes. - Before the rFVIIa injection, check that all abnormal parameters influencing rFVIIa efficacy (ie, acidosis, thrombocytopenia, hypofibrinogenemia, hypothermia, and hypocalcaemia) have been corrected. - If, 20 minutes after the first dose of rFVIIa, there is no response, administer a second dose of rFVIIa (90 µg/kg), ensuring before that temperature, acidemia, serum calcium, platelets, and fibrinogen have been optimized. - If bleeding persists after 2 doses of rFVIIa, consider hysterectomy. *List of relevant included studies:* Case series: Ahonen 2005, Segal 2004, Bouma 2008, Registry data: Alfirevic 2007, Isbister 2008, Sobieszczyk 2006, Barillari 2007 Comparative studies: Ahonen 2007, Hossain 2007 (both included in Module 5)				

CI, confidence interval; MA, meta-analysis; NA, not applicable; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review

Randomised controlled trials

STUDY DETAILS: Lavigne-Lissalde 2015			
Citation			
Lavigne-Lissalde, G., Aya, A. G., Mercier, F. J., Roger-Christoph, S., Chauleur, C., Morau, E., Ducloy-Bouthors, A. S., Mignon, A., Raucoules, M., Bongain, A., Boehlen, F., de Moerloose, P., Bouvet, S., Fabbro-Peray, P., & Gris, J. C. (2015). Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial. J Thromb Haemost, 13(4), 520-529. doi:10.1111/jth.12844 https://clinicaltrials.gov/ct2/show/record/NCT00370877			
Affiliation/Source of funds			
The study was supported by an Academic Research Clinical Trial grant by the French Ministry of Health (Programme Hospitalier Inter-Regional de Recherche Clinique, PHRC-I/2005/GL) A. G. Aya reports non-financial support from Novo Nordisk during the conduct of the study. A. Mignon reports lecture fees and grant support from Laboratoire Français Biopharmaceutique and non-financial support from Novo Nordisk during the conduct of the study.			
Study design	**Level of evidence**	**Location**	**Setting**
Randomised controlled trial	II	Eight university hospitals in France (7 locations) & Geneva, Switzerland February 2007 - November 2010	Multicentre, obstetrics and maternity
Intervention		**Comparator**	
60 µg/kg rhuFVIIa (Novoseven®) (single iv dose) (three patients did not receive full dose; one patient received more than recommended dose)		Standard of care (SoC) (patients assigned to SoC with very severe PPH received compassionate rhuFVIIa given late in an attempt to avoid emergency peripartum hysterectomy).	
Population characteristics			
Women (aged 18 yrs or older) with severe primary PPH, defined as the loss of more than 1500 mL of blood within 24 hr after birth (vaginal or caesarean) that persisted after sulprostone treatment. First-line therapies for PPH included: fluid resuscitation, bladder catheterization, manual removal of retained placenta, genital tract examination, uterine exploration, oxytocin (20–30 IU every 10–30 min) and one sulprostone infusion (500 µg within 1 hr). Median age 31 years; 14/84 (16/6%) twin pregnancies; 43/84 (51%) caesarean section delivery; 69/84 (82%) had neuraxial anaesthesia; PPH attributed to uterine atony 75/84 (89%).			
Length of follow-up		**Outcomes measured**	
Patients followed up to 5 days after PPH ended. Treatment success defined as estimated blood flow decreased to less than 50 mL per 10 minutes and within 30 minutes of randomisation.		The reduction of the need for specific second-line therapies, such as interventional haemostatic procedures, for blood loss and transfusions Mortality Thrombotic events (up to 5 days post infusion) * The contribution of any fluid used for washing was to be taken into account to prevent blood loss overestimation.	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: High *Description:* The study has plausible bias that seriously weakens confidence in the results. Study was not blinded, allowing for compassionate use of rFVIIa in the SoC arm (8/42 received late rFVIIa). It is possible that this introduced bias into the subsequent management of patients (e.g., second line therapies used). Primary outcome of volume of blood loss not available.			

STUDY DETAILS: Lavigne-Lissalde 2015				
RESULTS				
Population analysed	**Intervention**		**Comparator**	
Randomised	42		42	
Efficacy analysis (ITT)	42		42	
Efficacy analysis (PP)	42		42	
Safety analysis	42		42	
Outcome	**Intervention n/N (%) Median (IQR)**	**Comparator n/N (%) Median (IQR)**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
rFVIIa versus SoC				
Mortality N = 84	0/42 (0)	0/42 (0)	Not estimable	Not estimable
Transfusion volume, units, median (IQR) PRBCs N = 84	NR/42 (60) 2 (0, 3)	NR/42 (67) 2 (0, 4)	NR	No significant difference NR
Transfusion volume, units, median (IQR) FFP N = 84	NR/42 (45) 0 (0, 3)	NR/42 (48) 0 (0, 4)	NR	No significant difference NR
Transfusion volume, units, median (IQR) PC N = 84	NR/42 (26) NR	NR/42 (31) NR	NR	No significant difference NR
Morbidity Reduction in the need for specific second-line therapies (composite) N = 84	22/42 (52)	39/42 (93)	RR 0.56 (0.42, 0.76)	*Favours rFVIIa* $p < 0.0001$
Morbidity Arterial embolization N = 84	12/42 (29)	24/42 (57)	RR 0.50 (0.29, 0.86)	*Favours rFVIIa* $p = 0.0082$
Morbidity Arterial ligation N = 84	9/42 (21)	12/42 (29)	RR 0.75 (0.35, 1.59)	No significant difference $p = 0.45$
Morbidity Peripartum hysterectomy N = 84	3/42 (7)	8/42 (19)	RR 0.38 (0.11, 1.32)	No significant difference $p = 0.11$
Morbidity Other (B-lynch, Bakri Balloon etc.) N = 84	4/42 (10)	6/42 (14)	RR 0.67 (0.20, 2.19)	No significant difference $p = 0.50$
Safety Thrombotic events N = 84	2/42 (5)	0/42 (0)		No significant difference $p = 0.25$
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				

STUDY DETAILS: Lavigne-Lissalde 2015
Applicability (relevance of the evidence to the Australian health care system)
The evidence is directly applicable to the Australian healthcare context with few caveats
Additional comments
Authors conclusions: rFVIIa reduced the need for specific second line therapies in about one-third of patients, with the occurrence of non-fatal venous TEs in 1 in 20 patients. In a sub analysis, delivery mode did not affect the primary outcome.

CI, confidence interval; FFP, fresh frozen plasma; ITT, intent to treat; NA, not applicable; NR, not reported; PC, prothrombin concentrate; PP, per-protocol; PPH, primary postpartum haemorrhage; RBC, red blood cells; RCT, randomised controlled trial; rFVIIa, recombinant factor VIIa; SoC, standard of care

E6 Blood components (Question 6)

Systematic reviews/meta-analyses

<table>
<tr><td colspan="4">STUDY DETAILS: Warmuth 2012</td></tr>
<tr><td colspan="4">Citation</td></tr>
<tr><td colspan="4">WARMUTH, M., MAD, P. and WILD, C. (2012), Systematic review of efficacy and safety of fibrinogen substitution in adults. Acta Anaesthesiol Scand, 2012;56: 539-548</td></tr>
<tr><td colspan="4">Affiliation/Source of funds</td></tr>
<tr><td colspan="4">Conflicts of interest: The authors declared no conflicts of interest.
Funding: The study was funded by departmental funding only (Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria).
Author affiliations: Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location</td><td>Setting</td></tr>
<tr><td>SR and MA of RCTs (2) and observational studies (2)</td><td>I-III</td><td>In total, the studies were published in Denmark (1), Sweden (1) and Germany (2).
Studies related to PICO:
Rahe-Meyer 2009a: Germany
Rahe-Meyer 2009b: Germany</td><td>Surgical</td></tr>
<tr><td colspan="2">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="2">Rahe-Meyer 2009a and 2009b: Administration of fibrinogen concentrate prior to standard transfusion algorithm</td><td colspan="2">Rahe-Meyer 2009a and 2009b: Standard transfusion algorithm (PC and/or FFP if needed)</td></tr>
<tr><td colspan="4">Population characteristics</td></tr>
<tr><td colspan="4">Adult patients undergoing surgery with massive haemorrhage
SR not restricted to trauma.
Assessing FC in perioperative setting and massive haemorrhage. Two studies relevant to this review:
Rahe-Meyer 2009 - thoracoabdominal AA surgery (elective)
Rahe-Meyer 2009a - postoperative AV-AA</td></tr>
<tr><td colspan="2">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="2">Citations published between 1985 and May 2010.
Databases searched:
MEDLINE, EMBASE, the Centre for Reviews and Dissemination (CRD)-York databases [Database of Abstracts of Reviews of Effects (DARE), National Institute for Health Research Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database] and The Cochrane Library (from inception to 20 May 2010).</td><td colspan="2">Total concentrates of RBC, FFP, PC
Drainage volume
Number of patients with no transfusion
Safety including 30-day mortality</td></tr>
<tr><td colspan="4">INTERNAL VALIDITY</td></tr>
<tr><td colspan="4">Overall QUALITY of the systematic review (descriptive)</td></tr>
<tr><td colspan="4">Rating (AMSTAR): Low
Description: One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. Authors did not pool studies in the review and do not comment on why this was not performed.
Risk of bias of included studies: The overall quality of included studies was deemed to be poor. For the RCTs, the reasons were: inadequate method of randomisation; lack of information on allocation concealment; failure to sufficiently report comparability at baseline; no information about blinding of care providers, participants, or outcome assessors; incomplete outcome data; failure to analyse for intention to treat; selective reporting of outcomes and lack of information on determination of study size.</td></tr>
</table>

STUDY DETAILS: Warmuth 2012				
For the non-RCTs, the reasons for poor quality were: lack of information on allocation of groups; comparison of the intervention group with a historical control group; insufficient information about comparability of groups at baseline and at the analysis stage; questionable association between the reported outcomes and the received intervention (due to substitution of additional blood products such as RBC, FFP and PC); failure to blind care providers, participants and outcomes assessors; and lack of information on the determination of study size or an underpowered study.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[comparator]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
FC versus standard transfusion algorithm				
30-day mortality n = 33 (2 studies) Rahe-Meyer 2009a Rahe-Meyer 2009b	 0 0	 0 2/12 (17)	 NR NR	 NR NR
Total concentrates (U) n = 33 (2 studies) Rahe-Meyer 2009a Rahe-Meyer 2009b	 0.7 ± 1.5 (n = 10) 2.5 ± 4.3 (n = 6)	 8.2 ± 2.3 (n = 5) 16.4 ± 4.8 (n = 12)	 NR NR	 Favours FC *p* < 0.05 *p* < 0.05
RBC transfusion volume (U) in 24 hours n = 33 (2 studies) Rahe-Meyer 2009a Rahe-Meyer 2009b	 0.5 ± 1.1 (n = 10) 1.0 (n = 6)	 2.4 ± 1.1 (n = 5) 4.1 (n = 12)	 NR NR	 Favours FC *p* < 0.05 *p* < 0.05
FFP transfusion volume (U) in 24 hours n = 33 (2 studies) Rahe-Meyer 2009a Rahe-Meyer 2009b	 0.2 ± 0.6 (n = 10) 1.0 (n = 6)	 4.2 ± 1.1 (n = 5) 9.1 (n = 12)	 NR NR	 Favours FC *p* < 0.05 *p* < 0.05
PC concentrates (U) in 24 hours n = 33 (2 studies) Rahe-Meyer 2009a Rahe-Meyer 2009b	 0.0 (n = 10) 0.5 (n = 6)	 1.6 ± 0.9 (n = 5) 3.2 (n = 12)	 NR NR	 Favours FC *p* < 0.05 *p* < 0.05
Drainage volume (ml) n = 33 (2 studies) Rahe-Meyer 2009a Rahe-Meyer 2009b	 366 ± 199 (n = 10) 449 ± 182 (n = 6)	 716 ± 219 (n = 5) 1093 ± 594 (n = 12)	 NR NR	 Favours FC *p* < 0.05 *p* < 0.05
Number of patients with no transfusion n = 18 (1 study) Rahe-Meyer 2009b	 4/6 (67)	 0/12	 NR	 Favours FC *p* < 0.05
Re-exploration for bleeding n = 33 (2 studies) Rahe-Meyer 2009a Rahe-Meyer 2009b	 0/10 0/6	 1/5 (20) 4/12 (33)	 NR NR	 NR NR
Major neurological events n = 33 (2 studies)				

STUDY DETAILS: Warmuth 2012				
Rahe-Meyer 2009a	0/10	0/5	NR	NR
Rahe-Meyer 2009b	0/6	2/12 (17)	NR	NR
Renal failure n = 18 (1 study)				
Rahe-Meyer 2009b	0	2/12 (17)	NR	NR
Post-operative atrial fibrillation n = 33 (2 studies)				
Rahe-Meyer 2009a	1/10 (10)	1/5 (20)	NR	NR
Rahe-Meyer 2009b	0	1/12 (8)	NR	NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. Includes studies with surgical patients with massive haemorrhage.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context. The studies were conducted in developed European countries.				
Additional comments				
Author's conclusions: In conclusion, evidence from four poor quality, controlled trials suggests that the administration of fibrinogen concentrate improved clot firmness, decreased the need for other blood products and significantly reduced post-operative bleeding and drainage volume. In addition, it appeared to be safe. *List of relevant included studies:* Rahe-Meyer 2009a, Rahe-Meyer 2009b				

CI, confidence interval; FC, fibrinogen concentrate; FFP, fresh frozen plasma; NR, not reported; PC, platelet concentrate; PICO, population intervention comparator intervention; RBC, red blood cells; RCT, randomised controlled trial; SD, standard deviation; U, units.

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Aubron 2014			
Citation			
Aubron C, Reade M, C, Fraser J.F *et al*. Efficacy and safety of fibrinogen concentrate in trauma patients – a systematic review. *Journal of Critical Care*. 2014, 29: 471.e11-471.e17			
Affiliation/Source of funds			
Conflicts of interest: The authors declared no conflicts of interest. *Funding:* The study is part of a research program funded by the NHMRC. *Author affiliations:* AC and DJC affiliated with ANZIC Research Center, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC 3004, Australia. MCR affiliated with Australian Defence Force and Burns, Trauma and Critical Care Research Center, University of Queensland, Brisbane, QLD 4029, Australia. JFF affiliated with Critical Care Research Group, University of Queensland, Brisbane, QLD 4029, Australia. DJC was supported by an NHMRC Practitioner Fellowship. MCR is a serving officer in the Australian Defence Force. JF Fraser is supported by a Queensland Health Research Scholarship.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of 4 case reports and 7 retrospective studies (no meta-analysis). Only 1 study was a prospective observational study (Weiss 2011).	III-IV	Not reported	Trauma
Intervention		**Comparator**	
Schochl 2011: 6 g FC (median)		Schochl 2011: FFP	

STUDY DETAILS: Aubron 2014	
Nienaber 2011: 4 g FC (median) Wafaisade 2013: FC (dosage not reported) Innerhofer 2013: 25-50 mg/kg FC	Nienaber 2011: FFP Wafaisade 2013: no FC Innerhofer 2013: FC + FFP
Population characteristics	
Schochl 2011: ISS ≥ 16 and BE 2mmol/L or less. Abbreviated Injury Scale (AIS) of the abdomen, thorax, extremities ≥ 3. Nienaber 2011: ISS ≥ 16 and BE 2mmol/L or less upon ED admission and AIS of the abdomen, thorax, extremities ≥ 3. Wafaisade 2013: Trauma + ISS ≥ 16 at least 1 RBC + Trauma Associated Severe Haemorrhage (TASH) score ≥ 9. Innerhofer 2013: Trauma + ISS ≥ 15, multiple blunt injury, survival for at least 24 hours and need for haemostatic agents.	
Length of follow-up	**Outcomes measured**
Databases searched: MEDLINE, Cochrane Library (Citations published between Jan 2000 and April 2013).	Hospital mortality
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* There was no formal method for assessing risk of bias of included studies. The authors describe the limitation of the available literature - most studies are retrospective with small sample sizes, have a high degree of heterogeneity of the comparator, and heterogeneity in the measures of effect, the included studies lack rigorous analyses.	
RESULTS:	

Outcome **No. patients** **(No. trials)**	**Fibrinogen** **n/N (%)** **Mean ± SD**	**No fibrinogen** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
FC versus FFP				
Mortality, in-hospital overall N = 681 (2 studies) Schochl 2011 Nienaber 2011	 6/80 (7.5) 3/18 (16.7)	 10/601 (10) 2/18 (11.1)	 NR NR	 No significance difference *p* = 0.69 *p* = 0.50
Multi-organ failure N = 36 (1 study) Nienaber 2011	 3/18 (16.7)	 11/18 (61)	 NR	 *Favours FC* *p* = 0.015
RBC transfusion volume, units in first 6 hrs N = 36 (1 study) Nienaber 2011	 1 (NR) (n = 18)	 7.5 (NR) (n = 18)	 NR	 *Favours FC* *p* < 0.005
RBC transfusion volume, units in first 24 hrs, N = 36 (1 study) Nienaber 2011	median (IQR) 3 (0, 5) (n = 18)	median (IQR) 12.5 (8, 20) (n = 18)	 NR	 *Favours FC* *p* < 0.005
RBC transfusion volume, units, in first 48 hrs N = 681 (1 study) Schochl 2011	 2 (NR) (n = 80)	 3 (NR) (n = 601)	 NR	 NR
RBC transfusions volumes, units, overall N = 681 (1 study)				*Favours FC*

STUDY DETAILS: Aubron 2014				
Schochl 2011	57/80 (71)	583/601 (97)	NR	$p < 0.001$
Number of patients requiring platelets N = 717 (2 studies) Schochl 2011 Nienaber 2011	 7/80 (9) 0/18	 264/601 (44) 2/18 (11)	 NR NR	*Favours FC* $p < 0.001$ $p < 0.005$
PLT transfusion volume, units, overall N = 681 (1 study) Schochl 2011	 1 or 2 (n = 80)	 NR (n = 601)	 NR	 NR
FFP transfusion volume, units, overall N = 681 (1 study) Schochl 2011	 NA (n = 80)	 3 (n = 601)	 NR	 NR
FFP transfusion volume, units to 6 hours N = 36 (1 study) Nienaber 2011	 0 (n = 18)	 6 (n = 18)	 NR	 NA
FFP transfusion volume, units to 24 hours N = 36 (1 study) Nienaber 2011	 0 (n = 18)	 10 (n = 18)	 NR	 NA
PLT transfusion volume, units to 24 hrs N = 36 (1 study) Nienaber 2011	 0 (n = 18)	 2 (n = 18)	 NR	 $p < 0.005$
FC transfusion volume, units to 6 hrs N = 36 (1 study) Nienaber 2011	 4 (n = 18)	 0 (n = 18)	 NR	 NA
FC transfusion volume, units to 24 hours N = 36 (1 study) Nienaber 2011	 4 (n = 18)	 0 (n = 18)	 NR	 $p < 0.005$
FC transfusion volume, units, overall N = 681 (1 study) Schochl 2011	 6 (n = 80)	 NR (n = 601)	 NR	 NR
PCC transfusion volume, units to 6 hours N = 36 (1 study) Nienaber 2011	 1200 (n = 18)	 0 (n = 18)	 NR	 NA
PCC transfusion volume, units to 24 hours N = 36 (1 study) Nienaber 2011	 1200 (n = 18)	 0 (n = 18)	 NR	 NR
In-patient days N = 717 (2 studies) Schochl 2011 Nienaber 2011	 23 (n = 80) 26 (n = 18)	 32 (n = 601) 38 (n = 18)	 NR	 $p = 0.005$ $p = 0.481$

STUDY DETAILS: Aubron 2014				
ICU days N = 717 (2 studies) Schochl 2011 Nienaber 2011	 14.5 (n = 80) 19 (n = 18)	 14(n = 601) 16 (n = 18)	 NR	 No significant difference *p* = 0.95 *p* = 0.628
FC versus no FC				
6-hour mortality N = 588 (1 study) Wafaisade 2013	 31/294 (10.5)	 49/294 (16.7)	 NR	 *Favours FC* *p* = 0.03
24-hour mortality N = 588 (1 study) Wafaisade 2013	 41/294 (13.9)	 54/294 (18.4)	 NR	 *No significant difference* *p* = 0.15
Mortality 30 days N = 588 (1 study) Wafaisade 2013	 82/294 (27.9)	 73/294 (24.8)	 NR	 *No significant difference* *p* = 0.40
Mortality, in-hospital overall N = 588 (1 study) Wafaisade 2013	 84/294 (28.6)	 75/294 (25.5)	 NR	 *No significant difference* *p* = 0.40
Thromboembolic events N = 588 (1 study) Wafaisade 2013	 20/294 (6.8)	 10/294 (3.4)	 NR	 *No significant difference* *p* = 0.06
Multi-organ failure N = 588 (1 study) Wafaisade 2013	 180/294 (61.2)	 144/294 (49)	 NR	 *Favours FC* *p* = 0.003
Platelets, units N = 588 (1 study) Wafaisade 2013	 0 (n = 294)	 2 (1-3) (n = 294)	 NR	 *Favours FC* *p* < 0.005
RBC transfusion volume (units) N = 588 (1 study) Wafaisade 2013	 12.8 ± 14.3 (n = 294)	 11.3 ± 10.0 (n = 294)	 NR	 *No significant difference* *p* = 0.20
FFP transfusion volume (units) N = 588 (1 study) Wafaisade 2013	 10.6 ± 11.4 (n = 294)	 8.7 ± 8.2 (n = 294)	 NR	 *No significant difference* *p* = 0.07
In-patient days N = 588 (1 study) Wafaisade 2013	 34.6 ± 33.3 (n = 294)	 32.8 ± 28.4 (n = 294)	 NR	 *No significant difference* *p* = 0.68
ICU days N = 588 (1 study) Wafaisade 2013	 17.2 ± 17.6 (n = 294)	 17.3 ± 17.9 (n = 294)	 NR	 No significant difference *p* = 0.96
FC versus FC ± FFP				
Mortality 30 days N = 144 (1 study) Innerhofer 2013	5/66 (7.6)	6/78 (7.7.)	NR	No significant difference *p* = 0.979
Thromboembolism N = 144 (1 study) Innerhofer 2013	6/66 (10%)	6/78 (7.7)	NR	No significant difference *p* = 0.772

STUDY DETAILS: Aubron 2014				
Red blood cell transfusion volume, units N = 144 (1 study) Innerhofer 2013	(n = 66) 2 (0-6)	(n = 78) 7 (4-11)	NR	Favours FC ± PCC *p* < 0.001
Platelet transfusion volume, units N = 144 (1 study) Innerhofer 2013	(n = 66) 0	(n = 78) 1 (0-2)	NR	Favours FC ± PCC *p* < 0.001
In-patient days N = 144 (1 study) Innerhofer 2013	(n = 78) 29	(n = 78) 24	NR	No significant difference *p* = 0.074
ICU days N = 144 (1 study) Innerhofer 2013	(n = 78) 14	(n = 66) 12	NR	No significant difference *p* = 0.217
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. Weiss 2011, the only prospective observational study, included 28% trauma patients. It wasn't clear whether the non- patients had critical bleeding.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context. Weiss 2011 reported data from patients in German and Austrian hospitals, which are likely to be relevant to the Australian health system.				
Additional comments				
Authors conclusions: The authors conclude that despite methodological flaws, some of the available studies suggested that FC administration may be associated with a reduced blood product requirement. Randomised trials are warranted to determine whether FC improves outcomes in pre-hospital management of trauma patients or whether FC is superior to another source of fibrinogen in early hospital management of trauma patients. *List of relevant included studies:* Schochl 2011, Nienaber 2011, Wafaisade 2013, Innerhofer 2013				

AIS, abbreviated injury score; BE, base excess; CI, confidence interval; ED, emergency department; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ISS, injury severity score; NR, not reported; PCC, prothrombin complex concentrate; RBC, red blood cells; SD, standard deviation.

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Lunde 2014			
Citation			
LUNDE, J., STENSBALLE, J., WIKKELSØ, A., JOHANSEN, M. and AFSHARI, A. (2014), Fibrinogen concentrate for bleeding-a systematic review. Acta Anaesthesiol Scand, 58: 1061-1074. doi:10.1111/aas.12370			
Affiliation/Source of funds			
Conflicts of interest: The authors declared no conflicts of interest. *Funding:* The authors declared no funding for this review *Author affiliations:* Copenhagen University Hospital, Herlev Hospital, University of Copenhagen			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of RCTs (7) and observational studies (23)	I-III	Not reported	Obstetrics, trauma, surgery
Intervention		**Comparator**	
Non-RCT: Ahmed 2012: 4 g FC (mean)		Non-RCT: Ahmed 2012: CRYO	

STUDY DETAILS: Lunde 2014	
Bilicen 2013: 2 g FC (median) Innerhofer 2013: 57 mg/kg FC (median) Nienaber 2011: 4 g FC (median) Rahe-Meyer 2009: 7.8 g FC (mean) Wafaisade 2013: FC (dosage not stated)	Bilicen 2013: non-FC treatment Innerhofer 2013: FC + FFP Nienaber 2011: FFP treatment Rahe-Meyer 2009: FFP + PLT treatment Wafaisade 2013: non-FC treatment
Population characteristics	
Patients with bleeding requiring fibrinogen concentrate, indications including: Ahmed 2012: Postpartum haemorrhage Bilicen 2013: Surgery Innerhofer 2013: Trauma Nienaber 2011: Trauma Rahe-Meyer 2009: Cardiac surgery Wafaisade 2013: Trauma	
Length of follow-up	**Outcomes measured**
Databases searched: CENTRAL, MEDLINE, Internation Web of Science, CINAHL, LILACS (from inception to 9 August 2013) and Chinese Biomedical Literature Database (from inception to 10 November 2013).	RCT: Haemostatic conditions, e.g., achievement of haemostasis or coagulation parameters from either standard laboratory tests or ROTEM Transfusion of allogeneic blood products or safety (thromboembolic events) Non-RCTs: Reduction of bleeding Transfusion requirements Mortality
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The overall risk of bias for included RCTs was judged by the review authors to be high. There were concerns with small sample size, inadequate follow-up, missing intention to treat, lack of proper blinding and design based surrogate outcomes with high risk of bias. One study was only published as an abstract. Several studies used FC in conjunction with other pro-haemostatic factors. Six out of the seven RCTs were partially or fully funded by medical industry.	
RESULTS:	

Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneitya** **I^2 (*p*-value)**
FC versus FC ± FFP				
Mortality, 30 days n = 144 (1 study) Innerhofer 2013	5/66 (7.6)	6/78 (7.7)	NR	No significant difference *p* = 0.979
Multi-organ failure n = 144 (1 study) Innerhofer 2013	12/66 (18.2)	29/78 (37.2)	NR	*Favours FC* *p* = 0.015
Sepsis N = 144 (1 study) Innerhofer 2013	11/66 (16.7)	28/78 (35.9)	NR	*Favours FC* *p* = 0.014
Patients requiring blood transfusion	40/66 (60.6)	76/78 (97.4)	NR	*Favours FC* *p* < 0.001

STUDY DETAILS: Lunde 2014				
N = 144 (1 study) Innerhofer 2013				
RBC transfusion volume, units to 24 hrs N = 144 (1 study) Innerhofer 2013	Median (IQR) 2 (0, 6) (n = 66)	Median (IQR) 7 (4, 11) (n = 78)	NR	No significant difference *p* = 0.001
PLT transfusion volume, units to 24 hrs N = 144 (1 study) Innerhofer 2013	Median (IQR) 0 (0, 0) (n = 66)	Median (IQR) 8 (5, 10) (n = 78)	NR	NR
FC transfusion volume, units to 24 hrs N = 144 (1 study) Innerhofer 2013	Median (IQR) 4 (2, 4) (n = 66)	Median (IQR) 4 (2, 6) (n = 78)	NR	No significant difference *p* = 0.550
PCC transfusion volume, units to 24 hrs N = 144 (1 study) Innerhofer 2013	Median (IQR) 0 (0, 1200) (n = 66)	Median (IQR) 0 (0, 1200) (n = 78)	NR	No significant difference *p* = 0.001
RBC transfusion volume, units to 24 hrs N = 144 (1 study) Innerhofer 2013	Median (IQR) 7 (4, 11) (n = 66)	Median (IQR) 2 (0, 6) (n = 78)	NR	No significant difference *p* = 0.001
FFP transfusion volume, units to 24 hrs n = 144 (1 study) Innerhofer 2013	Median (IQR) 0 (0, 0) (n = 66)	Median (IQR) 8 (5, 10) (n = 78)	NR	NR
In-patient days n = 144 (1 study) Innerhofer 2013	 (n = 66) 29	 (n = 78) 24	NR	No significant difference *p* = 0.074
ICU days n = 144 (1 study) Innerhofer 2013	 (n = 66) 12	 (n = 78) 14	NR	No significant difference *p* = 0.217
FC versus FFP				
Mortality, overall, in-hospital n = 36 (1 study) Nienaber 2011	3/18 (16.7)	2/18 (11.1)	NR	No significant difference *p* = 0.500
Multi-organ failure n = 36 (1 study) Nienaber 2011	3/18 (16.7)	11/18 (61.1)	NR	*Favours FC* *p* = 0.015
Red blood cell (units) transfusion volume n = 36 (1 study) Nienaber 2011	(n = 18) 3	(n = 18) 12.5	NR	*Favours FC* *p* < 0.005
In-patient days n = 36 (1 study) Nienaber 2011	(n = 18) 26	(n = 18) 38	NR	No significant difference *p* = 0.481
ICU days n = 36 (1 study) Nienaber 2011	(n = 18) 19	(n = 18) 1	NR	No significant difference *p* = 0.628

STUDY DETAILS: Lunde 2014				
FC versus FFP + PLT				
Mortality, 30-day n = 18 (1 study) Rahe-Meyer 2009	0/6	2/12 (17)	NR	NR
Re-exploration for bleeding n = 18 (1 study) Rahe-Meyer 2009	0/6	4/12 (33)	NR	NR
Postoperative atrial fibrillation n = 18 (1 study) Rahe-Meyer 2009	0/6	1/12 (8)	NR	NR
Renal failure n = 18 (1 study) Rahe-Meyer 2009	0/6	2/12 (17)	NR	NR
Major neurologic events n = 18 (1 study) Rahe-Meyer 2009	0/6	2/12 (17)	NR	NR
Blood transfusion volume (units) n = 18 (1 study) Rahe-Meyer 2009	(n = 6) 2.5	(n = 12) 16.4	NR	NR
RBC transfusion volume, units to 24 hours n = 18 (1 study) Rahe-Meyer 2009	(n = 6) 1.0	(n = 12) 4.1	NR	NR
RBC transfusion volume, mL to 24 hours N = 18 (1 study) Rahe-Meyer 2009	(n = 6) 449.2	(n = 12) 1092.5	NR	NR
FFP transfusion volume, units to 24 hours N = 18 (1 study) Rahe-Meyer 2009	(n = 6) 1.0	(n = 12) 9.1	NR	*Favours FC* $p < 0.05$
PLT transfusion volume, units, to 24 hours N = 18 (1 study) Rahe-Meyer 2009	(n = 6) 0.5	(n = 12) 3.2	NR	*Favours FC* $p < 0.05$
ICU days N = 18 (1 study) Rahe-Meyer 2009	(n = 6) 37 ± 18.9	(n = 12) 115.4 ± 60.2	NR	*Favours FC* $p < 0.05$
FC versus non-FC treatment				
Mortality (6-hour) N = 588 (1 study) Wafaisade 2013	31/294 (10.5)	49/294 (16.7)	NR	NR
Mortality (24 h) N = 588 (1 study) Wafaisade 2013	NR/294	NR/294	NR	No significant difference NR
Mortality (30 day) N = 588 (1 study) Wafaisade 2013	NR/294	NR/294	NR	No significant difference NR

STUDY DETAILS: Lunde 2014				
Mortality, 30 day N = 1075 (1 study) Bilecen 2013	18/264 (7)	33/811 (4)	0.96 (0.48, 1.92)	NR
Multi-organ failure N = 588 (1 study) Wafaisade 2013	180/294 (61.2)	144/294 (49)	NR	*Favours FC* *p* = 0.003
Myocardial infarction N = 1075 (1 study) Bilecen 2013	14/264 (5)	30/811 (4)	1.10 (0.53, 2.27)	*No significant difference* *p* = 0.07
Cerebrovascular accident/ transient ischemic attack N = 1075 (1 study) Bilecen 2013	11/264 (5)	30/811 (4)	1.16 (0.50, 2.72)	No significant difference *p* = 0.15
Renal insufficiency/ failure N = 1075 (1 study) Bilecen 2013	13/264 (5)	38/811 (5)	0.62 (0.29, 1.32)	No significant difference *p* = 0.87
Total infections N = 1075 (1 study) Bilecen 2013	29/264 (11)	74/811 (9)	1.18 (0.72, 1.95)	No significant difference *p* = 0.37
Red blood cell (units) transfusion volume N = 588 (1 study) Wafaisade 2013	(n = 294) 12.8 ± 14.3	(n = 294) 11.3 ± 10.0	NR	No significant difference *p* = 0.20
FFP (units) transfusion volume N = 588 (1 study) Wafaisade 2013	(n = 294) 10.6 ± 11.4	(n = 294) 8.7 ± 8.2	NR	No significant difference *p* = 0.07
In-patient days N = 588 (1 study) Wafaisade 2013	(n = 294) 34.6 ± 33.3	(n = 294) 32.8 ± 28.4	NR	No significant difference *p* = 0.96
ICU days N = 588 (1 study) Wafaisade 2013	(n = 294) 17.2 ± 17.6	(n = 294) 17.3 ± 17.9	NR	No significant difference *p* = 0.68
FC versus CRYO				
RBC transfusion volume (units) N = 34 (1 study) Ahmed 2012	(n = 20) 5.90 (0.96)	(n = 14) 7.21 (1.23)	NR	No significant difference *p* = 0.40
FFP transfusion volume (units) N = 34 (1 study) Ahmed 2012	mean (SEM) 3.15 (0.65) (n = 20)	mean (SEM) 4.07 (0.74) (n = 14)	NR	No significant difference *p* = 0.36
PLT transfusion volume (units) n = 34 (1 study) Ahmed 2012	mean (SEM) 1.00 (0.30) (n = 20)	mean (SEM) 1.00 (0.36) (n = 14)	NR	No significant difference *p* = 0.99
FC transfusion volume (units) n = 34 (1 study)	mean (SEM) 3.34 (0.22) (n = 20)	mean (SEM) 3.05 (0.19) (n = 14)	NR	No significant difference *p* = 0.35

STUDY DETAILS: Lunde 2014				
Ahmed 2012				
In-patient days n = 34 (1 study) Ahmed 2012	mean (SEM) 6.55 (0.81) (n = 20)	mean (SEM) 5.21 (0.33) (n = 14)	NR	No significant difference *p* = 0.19
HDU hours n = 34 (1 study) Ahmed 2012	mean (SEM) 33.6 (5.44) (n = 20)	mean (SEM) 34.1 (4.32) (n = 14)	NR	No significant difference *p* = 0.95
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. Included studies contain bleeding patients due to post-partum haemorrhage, cardiac and non-cardiac surgy and trauma.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. Study locations for the included studies are not reported.				
Additional comments				
Author's conclusions: Weak evidence from RCTs supports the use of fibrinogen concentrate in bleeding patients, primarily in elective cardiac surgery. However, a general use of fibrinogen across all settings is only supported by non-RCTs with serious methodological shortcomings. *List of relevant included studies:* Ahmed 2012, Bilicen 2013, Innerhofer 2013, Nienaber 2011, Rahe-Meyer 2009, Wafaisade 2013				

CI, confidence interval; FC, fibrinogen concentrate; FFP, fresh frozen plasma; NR, not reported; PLT, platelets; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SD, standard deviation; SEM, standard error of mean;

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Mengoli 2017			
Citation			
Mengoli, C., Franchini, M., Marano, G., Pupella, S., Vaglio, S., Marietta, M., & Liumbruno, G. M. (2017). The use of fibrinogen concentrate for the management of trauma-related bleeding: a systematic review and meta-analysis. Blood transfusion = Transfus 2017, 15(4), 318–324. doi:10.2450/2017.0094-17			
Affiliation/Source of funds			
Conflicts of interest: The authors declared no conflicts of interest except for GML, who is the Editor-in-Chief of Blood Transfusion and this manuscript had undergone additional review as a result. *Funding:* Details on funding not provided. *Author affiliations:* CM, MF, GM, SP, SV and SML affiliated with Italian National Blood Centre, National Institute of Health, Rome. MF affiliated with Department of Haematology and Transfusion Medicine, "Carlo Poma" Hospital, Mantua. SV affiliated with Department of Clinical and Molecular Medicine, "Sapienza" University of Rome, Rome. MM affiliated with Department of Oncology, Haematology and Respiratory Diseases, University Hospital, Modena, Italy.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of prospective (1) and retrospective (6) studies	I-III	Not reported	Trauma
Intervention		**Comparator**	
Schochl 2011: 6 g FC (median) Nienaber 2011: 4 g FC (median) Innerhofer 2013: 2g FC, 4g FC + FFP Wafaisade 2013: FC (dose not reported)		Schochl 2011: FFP Nienaber 2011: FFP Innerhofer 2013: FC+FFP Wafaisade 2013: no FC	
Population characteristics			
Patients with trauma-related bleeding (severe trauma)			

STUDY DETAILS: Mengoli 2017	
Length of follow-up	**Outcomes measured**
Databases searched: MEDLINE, EMBASE and SCOPUS (from Jan 2000 to Feb 2017).	Mortality (overall in-hospital, 6 hours, 24 hours, 72 hours) Transfusion requirements (RBC, platelets) Laboratory coagulation parameters Clinical outcomes (sepsis, multi-organ failure, days of ventilation, duration of hospitalisation, thromboembolic events)
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and *may not* provide an accurate and comprehensive summary of the available studies that address the question of interest. Results were pooled if outcome reported in at least three studies. *Risk of bias of included studies:* The quality of evidence of the seven studies evaluated was poor, according to GRADE criteria. All studies were retrospective, except Weiss 2011. All were cohort studies, in which the treatment allocation was an observed (post-hoc) exposure, instead of a randomised controlled trial or quasi-experimental studies with predetermined eligibility criteria and prior allocation. No study was randomised.	
RESULTS:	

Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneitya** **I2 (*p*-value)**
FC versus FFP				
Mortality, overall, in-hospital N = 717 (2 studies) Schochl 2011 Nienaber 2011	 NR/80 NR/18	 NR/601 NR/18	 RR 0.75 (0.34, 1.68) RR 1.50 (0.28, 7.93)	 NR NR
MOF N = 36 (1 study) Schochl 2011	3/18 (16.7)	11/18 (61)	NR	*Favours FC* *p* = 0.015
Sepsis N = 36 (1 study) Schochl 2011	3/18 (16.7)	6/18 (33.3)	NR	No significant difference *p* = 0.443
Number of patients requiring RBC units N = 681 (1 study) Schochl 2011	57/80 (71%)	583/601 (97%)	NR	*Favours FC* *p* < 0.001
Number of patients requiring platelets N = 681 (1 study) Schochl 2011	7/80 (9%)	264/601 (44%)	NR	*Favours FC* *p* < 0.001
Red blood cell (units) transfusion volume N = 36 (1 study) Nienaber 2011	(n = 18) 3	(n = 18) 12.5	NR	*Favours FC* *p* < 0.005
In-patient days N = 717 (2 studies) Schochl 2011 Nienaber 2011	Median (IQR) (n = 98) 23 (14.5, 40.5) 26 (19, 50)	Median (IQR) (n = 619) 32 (20, 49) 38 (21, 48)	NR	 *p* = 0.005, *Favours FC* *p* = 0.481, No difference

STUDY DETAILS: Mengoli 2017				
ICU days N = 717 (2 studies) Schochl 2011 Nienaber 2011	Median (IQR) (n = 98) 14.5 (8.5, 21) 19 (9, 33)	Median (IQR) (n = 619) 14 (6, 23) 16 (13, 25)	NR	 No significant difference *p* = 0.95 *p* = 0.628
FC versus no FC				
Mortality, overall, in-hospital N = 588 (1 study) Wafaisade 2013	NR/294	NR/294	RR 1.12 (0.86, 1.46)	NR
Mortality, 6-hour N = 588 (1 study) Wafaisade 2013	31/294 (10.5%)	49/294 (16.7%)	NR	*Favours FC* *p* = 0.03
Multiple organ failure N = 588 (1 study) Wafaisade 2013	180/294 (61.2%)	144/294 (49%)	NR	*Favours FC* *p* = 0.003
Thromboembolic events N = 588 (1 study) Wafaisade 2013	20/294 (6.8%)	10/294 (3.4%)	NR	No significant difference *p* = 0.06
RBC transfusion volume, units N = 588 (1 study) Wafaisade 2013	(n = 294) 12.8 ± 14.3	(n = 294) 11.3 ± 10.0	NR	No significant difference *p* = 0.20
FFP transfusion volume, units N = 588 (1 study) Wafaisade 2013	(n = 294) 10.6 ± 11.4	(n = 294) 8.7 ± 8.2	NR	No significant difference *p* = 0.07
In-patient days N = 588 (1 study) Wafaisade 2013	(n = 294) 34.6 ± 33.3	(n = 294) 32.8 ± 28.4	NR	No significant difference *p* = 0.96
ICU days N = 588 (1 study) Wafaisade 2013	(n = 294) 17.2 ± 17.6	(n = 294) 17.3 ± 17.9	NR	No significant difference *p* = 0.68
FC versus FC ± FFP				
Mortality, 30 days N = 144 (1 study) Innerhofer 2013	5/66 (7.6)	6/78 (7.7)	NR	No significant difference *p* = 0.979
Thromboembolism N = 144 (1 study) Innerhofer 2013	6/66 (10)	6/78 (7.7)	NR	No significant difference *p* = 0.772
Sepsis N = 144 (1 study) Innerhofer 2013	11/66 (16.7)	28/78 (35.9)	NR	No significant difference *p* = 0.014
MOF N = 144 (1 study) Innerhofer 2013	12/66 (18.2)	29/78 (37.2)	NR	No significant difference *p* = 0.015
RBC transfusion volume, units to 24 hrs	Median (IQR)	Median (IQR)	NR	*Favours FC ± PCC* *p* < 0.001

STUDY DETAILS: Mengoli 2017				
N = 144 (1 study) Innerhofer 2013	2 (0, 6) (n = 66)	7 (4, 11) (n = 78)		
Platelet transfusion volume, units to 24 hrs N = 144 (1 study) Innerhofer 2013	Median (IQR) 0 (0, 0) (n = 66)	Median (IQR) 0 (0, 1) (n = 78)	NR	*Favours FC ± PCC* *p* = 0.003
In-patient days N = 144 (1 study) Innerhofer 2013	Median (IQR) 24 (12, 35) (n = 66)	Median (IQR) 29 (16, 50) (n = 78)	NR	No significant difference *p* = 0.074
ICU days N = 144 (1 study) Innerhofer 2013	Median (IQR) 12 (6, 24) (n = 66)	Median (IQR) 14 (7, 30) (n = 78)	NR	No significant difference *p* = 0.217
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. Studies included patients with trauma-related bleeding. However, it is not clear what proportion of patients in all the included trials were trauma patients as Weiss 2011 had only 28% trauma patients.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The setting for the included trials are not provided.				
Additional comments				
Authors conclusions: Although the meta-analytic pooling of the current literature evidence suggests no beneficial effect of fibrinogen concentrate in the setting of severe trauma, the quality of data retrieved was poor and the final results of ongoing randomised trials will help to further elucidate the role of fibrinogen concentrate in traumatic bleeding. *List of relevant included studies:* Schochl 2011, Nienaber 2011, Innerhofer 2013, Wafaisade 2013				

CI, confidence interval; FC, fibrinogen concentrate; FFP, fresh frozen plasma; NR, not reported; PCC, prothrombin complex concentrate; RBC, red blood cells; RR, relative risk; SD, standard deviation.

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Fabes 2018
Citation
Fabes 2018 Fabes J, Brunskill SJ, Curry N, Doree C, Stanworth SJ. Pro-coagulant haemostatic factors for the prevention and treatment of bleeding in people without haemophilia. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD010649. DOI: 10.1002/14651858.CD010649.pub2.
Affiliation/Source of funds
Conflicts of interest: The authors did not address potential conflicts of interest. The views and the opinions expressed are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health. *Funding:* This project was supported by the UK National Institute for Health Research, through Cochrane Infrastructure funding to the Cochrane Injuries Group. *Author affiliations:* JF affiliated with John Radcliffe Hospital, Oxford, UK. SJB and CD affiliated with Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. NC affiliated with Oxford Haemophilia & Thrombosis Centre, Churchill Hospital, Oxford, UK. SJS affiliated with National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford, UK.

STUDY DETAILS: Fabes 2018			
Study design	**Level of evidence**	**Location**	**Setting**
SR and MA of 31 randomised controlled trials (from 61 references)	I	Three trials were multicentre, multinational and six were multicentre based in a single country (Germany, Spain, UK, Sweden, Denmark) 22 trials were single centre in Iran (4), Germany (3), Switzerland (3), Netherlands (2), Brazil (1), Austria (1), Canada (1), China (1), Denmark (1), Great Britain (1), Italy (1), Japan (1), Sweden (1), USA (1). Studies relevant to PICO: Bilicen 2017: Netherlands Collins 2017: UK Curry 2018: UK Jeppsson 2016: Sweden Nascimento 2016: Canada Rahe-Meyer 2013: Germany Rahe-Meyer 2016: Germany Wikkelso 2015: Denmark Galas 2014: Brazil Innerhofer 2017: Austria Lance 2012: Netherlands Tanaka 2014: USA	In total, 22 trials were in an elective surgical setting. 5 trials in an urgent medical setting. 4 trials in a non-urgent medical setting Studies relevant to PICO: Bilicen 2017: Cardiac surgery Collins 2017: Obstetrics Curry 2018: Trauma Jeppsson 2016: Cardiac surgery Nascimento 2016: Trauma Rahe-Meyer 2013: Cardiac surgery Rahe-Meyer 2016: Cardiac surgery Wikkelso 2015: Obstetrics Galas 2014: Paediatric cardiac surgery Innerhofer 2017: Trauma Lance 2012: Surgery Tanaka 2014: Surgery
Intervention		**Comparator**	
Bilicen 2017: FC (dose calculated by participant's weight) Collins 2017: FC (variable dose with aim to increase FIBTEM A5 to > 22 mm in the fibrinogen arm) Curry 2018: 6g FC Jeppsson 2016: 2g FC Nascimento 2016: 6g FC Rahe-Meyer 2013: FC (median 8g ranging from 6g to 9g) Rahe-Meyer 2016: FC Wikkelso 2015: 2g FC over 20 minutes in 100 mL sterile water Galas 2014: 60 mg/kg FC Innerhofer 2017: 50 mg/kg FC Lance 2012: 2U FFP + 2g FC as a consequence of massive bleeding during or after surgery Tanaka 2014: 4g FC within 30 minutes of intervention decision		Bilicen 2017: Placebo (albumin in 0.9% saline) Collins 2017: 0.9% saline Curry 2018: 0.9% saline Jeppsson 2016: 0.9% saline Nascimento 2016: 0.9% saline Rahe-Meyer 2013: 0.9% saline Rahe-Meyer 2016: 0.9% saline Wikkelso 2015: 100 mL isotonic saline Galas 2014: 10 mL/kg CP Innerhofer 2017: 15 mL/kg FFP Lance 2012: 4U FFP as a consequence of massive bleeding during or after surgery Tanaka 2014: 1 U apheresis platelets (median 230 mL) within 30 minutes of intervention decision	
Population characteristics			
Bilicen 2017: Adults over 18 years of age undergoing elective high-risk cardiac surgery Collins 2017: Women aged 18 years and above ≥ 24 weeks gestation with major postpartum haemorrhage Curry 2018: Adults aged 16 years and above with active bleeding and in haemorrhagic shock requiring activation of MTP or received emergency RBC transfusion			

STUDY DETAILS: Fabes 2018				
Nascimento 2016: Aged 18 years and above with severe trauma (blunt or penetrating) at risk of significant haemorrhage by systolic arterial pressure < 100mmHg and requiring un-crossmatched RBS any time from injury until 30 minutes after hospital arrival Rahe-Meyer 2013: Aged 18 or above with elective aortic valve replacement surgery Rahe-Meyer 2016: Aged 18 or above with first 5 minutes bleeding mass of 60 – 250 g; body temperature ≥ 37.5 degrees Celsius. Wikkelso 2015: Aged > 18 years with postpartum haemorrhage defined as bleeding from the uterus or birth canal or both, within 24 hours postpartum, C-section with estimated perioperative blood loss >1 L or vaginal delivery with estimated blood loss > 0.5 L Galas 2014: Patients age under 15 years undergoing cardiac surgery cardiopulmonary bypass, intra-operative bleeding and hypofibrinogenaemia Innerhofer 2017: Adults (aged 18-80 years) with TSS > 15 and clinical signs or risk of substantial haemorrhage Lance 2012: 307 patients aged 18 years and above admitted for cardiovascular, major abdominal or orthopaedic surgery expected to last ≥ 120 minutes (255 patients did not meet the criteria for massive haemorrhage). Tanaka 2014: Elective cardiopulmonary bypass procedures. If haemostatic condition of surgical field either moderate bleeding or severe then randomly assigned to trial intervention.				
Length of follow-up			**Outcomes measured**	
Databases searched: CENTRAL, MEDLINE, Embase, CINAHL, PubMed, PROSPERO, Transfusion Evidence Library, LILACS, IndMed, KoreaMed, Web of Science Conference Proceedings Citation Index, ClinicalTrials.gov, EUDRACT, WHO International Clinical Trials Registry Platform, ISRCTN Register (from inception to 18 April 2018).			Transfusion requirement Blood loss Multi-organ failure Clotting time	
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* The overall quality of the evidence ranged from very low to high, with most trial outcomes being rated as low quality. No trial was at low risk of bias in all domains, but the authors downgraded half the outcomes by one level for risk of bias. Domains with high risk of bias included allocation concealment, blinding of study personnel and outcome assessors, incomplete outcome data and selective reporting. The small cohorts and rare mortality and thrombotic events introduced risks of imprecision. Lastly, the trials in this review represented most of the clinical areas in which bleeding is observed, but not all clinical areas were represented in each of the intervention comparisons. Moreover, the trials did not set out to explore the outcomes of interest to this review, and this introduced inconsistency				
RESULTS:				
Outcome **No. patients (No. trials)**	**FC** **n/N (%)** **Mean ± SD**	**No FC** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
FC vs inactive control				
Mortality (all cause), up to 28 days N = 97 (2 studies) Curry 2018 Nascimento 2016	13/48 (27) 10/24 (42) 3/24 (12.5)	9/49 (18) 7/24 (29) 2/25 (8)	RR 1.46 (0.71, 2.99) RR 1.43 (0.65, 3.13) RR 1.56 (0.29, 8.55)	*No significant difference* *p* = 0.30 No significant heterogeneity I^2 = 0.0%
Mortality (all-cause), up to 30 days N = 120 (1 study) Bilicen 2017	2/60 (3.3)	0/60	RR 5.00 (0.25, 102.00)	*No significant difference* *p* = 0.30
Mortality (all-cause), up to 6 weeks postnatally	0/149	0/145	Not estimable	not estimable

STUDY DETAILS: Fabes 2018				
N = 294 (2 studies) Collins 2017 Wikkelso 2015	 0/26 0/123	 0/24 0/121		
Mortality (all-cause), up to 46 days post-operative N = 213 (2 studies) Rahe-Meyer 2013 Rahe-Meyer 2016	2/107 (1.9) 1/29 (3.4) 1/78 (1.3)	9/106 (8.5) 4/32 (12.5) 5/74 (6.8)	RR 0.23 (0.05, 1.01) RR 0.28 (0.03, 2.33) RR 0.19 (0.02, 1.59)	*No significant difference* *p* = 0.052 No significant heterogeneity I^2 = 0.0%
Mortality due to bleeding up to 28 days N = 93 (2 studies) Curry 2018 Nascimento 2016	3/45 (6.7) 2/24 (8.3) 1/21 (4.7)	1/48 1/24 (4.2) 0/24	RR 2.45 (0.38, 15.76) RR 2.00 (0.19, 20.61) RR 3.41 (0.15, 79.47)	*No significant difference* *p* = 0.35 No significant heterogeneity I^2 = 0.0%
Mortality due to bleeding up to 6 weeks postnatally N = 294 (2 studies) Collins 2017 Wikkelso 2015	0/149 0/26 0/123	0/145 0/24 0/121	Not estimable Not estimable Not estimable	Not estimable
Mortality due to bleeding up to 46 days N = 152 (1 study) Rahe-Meyer 2016	 0/78	 0/78	 Not estimable	Not estimable
Arterial thromboembolic events up to 28 days N = 84 (2 studies) Curry 2018 Nascimento 2016	 1/20 (5) 0/21	 2/19 (10.5) 0/24	 RR 0.48 (0.05, 4.82) Not estimable	 NR Not estimable
Arterial thromboembolic events up to 30 days N = 120 (1 study) Bilicen 2017	 7/60 (11.7)	 3/60 (5)	 RR 2.33 (0.63, 8.60)	NR
Arterial thromboembolic events up to 45 days N = 61 (1 study) Rahe-Meyer 2013	 1/29 (3.4)	 1/32 (3.1)	 RR 1.10 (0.07, 16.85)	NR
Arterial thromboembolic events up to 6 weeks postnatal N = 294 (2 studies) Collins 2017 Wikkelso 2015	 0/26 0/123	 0/24 0/121	 Not estimable Not estimable	 Not estimable Not estimable
Venous thromboembolic events up to 28 days N = 39 (1 study) Curry 2018	 2/20 (10)	 0/19	 RR 4.79 (0.24, 93.19)	NR

STUDY DETAILS: Fabes 2018				
Venous thromboembolic events up to 30 days N = 120 (1 study) Bilicen 2017	0/60	0/60	Not estimable	Not estimable
Venous thromboembolic events up to 45 days N = 61 (1 study) Rahe-Meyer 2013	0/29	1/32 (3.1%)	RR 0.37 (0.02, 8.66)	NR
Venous thromboembolic events up to 6 weeks postnatally N = 294 (2 studies) Collins 2017 Wikkelso 2015	1/26 (3.8) 0/123	1/24 (4.2) 0/121	RR 0.92 (0.06, 13.95) Not estimable	NR Not estimable
Allergic adverse events up to 24 hours N = 244 (1 study) Wikkelso 2015	0/123	1/121 (0.83)	RD -0.01 (-0.03, 0.01)	NR
Allergic adverse events up to 10 days N = 61 (1 study) Rahe-Meyer 2013	0/29	0/32	RD 0.0 (-0.06, 0.06)	Not estimable
Allergic adverse events up to 28 days N = 45 (1 study) Nascimento 2016	0/21	0/24	RD 0.0 (-0.08, 0.08)	Not estimable
Allergic adverse events up to 30 days N = 120 (1 study) Bilicen 2017	0/60	0/60	RD 0.0 (-0.03, 0.03)	Not estimable
FC vs FFP				
Mortality (all-cause) up to 30 days N = 137 (2 studies) Lance 2012 Innerhofer 2017	1/22 (4.5) 5/50 (10)	1/21 (4.8) 2/44 (4.5)	OR 0.95 (0.06, 14.30) OR 2.20 (0.45, 10.78)	NR NR
Mortality due to bleeding N = 137 (2 studies) Lance 2012 Innerhofer 2017	0/22 0/50	0/21 0/44	Not estimable Not estimable	No significant heterogeneity I^2 = 0.0% not estimable not estimable
Arterial thromboembolic events N = 43 (1 study) Lance 2012	1/22 (4.5)	0/21	RR 2.87 (0.12, 66.75)	NR
Venous thromboembolic events				

STUDY DETAILS: Fabes 2018				
N = 137 (2 studies) Lance 2012 Innerhofer 2017	1/22 (4.5) 7/50 (14)	0/21 9/44 (20.5)	RR 3.00 (0.12, 77.83) RR 0.63 (0.21, 1.87)	NR NR
RBC transfusion requirement N = 43 (1 study) Lance 2012	(n = 22) 1494 (SD 714)	(n = 21) 1614 (SD 714)	MD -120.00 (-546.93, 306.93)	NR
Allergic adverse events N = 43 (1 study) Lance 2012	0/22	0/21	Not estimable	not estimable
FC vs CP				
Mortality (all-cause) up to 7 days N = 63 (1 study) Galas 2014	0/30	0/33	Not estimable	not estimable
Mortality due to bleeding up to 7 days N = 63 (1 study) Galas 2014	0/30	0/33	Not estimable	not estimable
Arterial thromboembolic events N = 63 (1 study) Galas 2014	2/30 (6.7)	5/33 (12.2)	RR 0.44 (0.09, 2.10)	NR
Venous thromboembolic events N = 63 (1 study) Galas 2014	0/30	0/33	Not estimable	not estimable
Allergic adverse events N = 63 (1 study) Galas 2014	0/30	0/33	Not estimable	Not estimable
FC vs PLT				
Mortality (all-cause) up to 28 days N = 20 (1 study) Tanaka 2014	0/10	0/10	Not estimable	Not estimable
Arterial thromboembolic events N = 20 (1 study) Tanaka 2014	0/10	1/10 (10)	RR 0.33 (0.02, 7.32)	NR
Venous thromboembolic events N = 20 (1 study) Tanaka 2014	0/10	0/10	Not estimable	Not estimable
Mortality due to bleeding N = 20 (1 study) Tanaka 2014	0/10	0/10	Not estimable	Not estimable
Postoperative atrial fibrillation N = 18 (1 study) Tanaka 2014	0/6	1/12 (8)	Not estimable	Not estimable

STUDY DETAILS: Fabes 2018				
Renal failure N = 18 (1 study) Tanaka 2014	0/6	2/12 (17)	Not estimable	Not estimable
Major neurologic events N = 18 (1 study) Tanaka 2014	0/6	2/12 (17)	Not estimable	Not estimable
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context				
Additional comments				
Authors conclusions: The inadequate quality of evidence in most of the studies included in the review means that conclusions cannot be drawn for clinical practice of the use of the interventions outside controlled trials. *List of included relevant trials:* Bilicen 2017, Collins 2017, Curry 2018, Jeppsson 2016, Nascimento 2016, Rahe-Meyer 2013, Rahe-Meyer 2016, Wikkelso 2015, Galas 2014, Innerhofer 2017, Lance 2012, Tanaka 2014				

CI, confidence interval; CP, cryoprecipitate; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ITT, intention-to-treat; MD, mean difference; MTP, massive transfusion protocol; NR, not reported; OR, odd ratio; PICO, patient, intervention, comparator, outcome; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RD, risk difference; RR, relative risk; SD, standard deviation; U, unit; UK, United Kingdom; US, United States

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: McQuilten 2018			
Citation			
McQuilten ZK, Crighton G, Brunskill S, *et al*. Optimal dose, timing and ratio of blood products in massive transfusion: Results from a systematic review. *Transfusion Medicine Reviews*. 2018, 32: 6–15			
Affiliation/Source of funds			
Conflicts of interest: Zoe McQuilten, Erica Wood, Neil Waters, Tania Richter and Jess Morison are employed by Monash University, whose Transfusion Research Unit has received financial support from Australian Red Cross Blood Service, New Zealand Blood Service, the Victorian Department of Health and CSL Behring for the Australian and New Zealand Massive Transfusion Registry. *Funding:* Funding support from Australian National Blood Authority. McQuilten received funding support from National Health and Medical Research Council (NHMRC) Early Career Fellowship and NHMRC Centre for Research Excellence in Patient Blood Management in Critical Care and Trauma. Transfusion Research Unit of Monash University received financial support from Australian Red Cross Blood Service, New Zealand Blood Service, Victorian Department of Health and CSL Behring for the Australian and New Zealand Massive Transfusion Registry. *Author affiliations:* ZKM, GC, JKM, THR, NW and EMW affiliated with Transfusion Research Unit, Monash University. ZKM affiliated with Australian and New Zealand Intensive Care Research Centre. SB affiliated with Systematic Reviews Initiative, NHS Blood and Transplant/Oxford University Hospitals NHS Trust.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs (6 completed studies, 10 ongoing)	I	In total, the included trials were performed in North America (1), UK (1) and not reported (4) Studies relevant to PICO: Nascimento 2016: Canada Curry 2015: UK	Trauma centre

Intervention	**Comparator**
Blood component therapy (FFP, platelets, CRYO, or fibrinogen concentrate) to RBCs Nascimento 2016: Fibrinogen concentrate 6 g IV within 30 minutes after randomisation Curry 2015: early CRYO + standard therapy (massive haemorrhage protocol)	Dose, timing ratio comparisons Nascimento 2016: Placebo (normal saline) Curry 2015: Standard therapy (6 U RBC and 4 U FFP, and TXA)
Population characteristics	
Paediatric and/or adult who had critical bleeding and had received, or was anticipated to receive, a massive transfusion and measured at least one outcome of interest. Nascimento 2016: Patients at risk for significant haemorrhage evidenced by systolic blood pressure <100 mmHg and requiring uncrossmatched RBC transfusion at any time from injury until 30 minutes after hospital arrival. Curry 2015: Patients ≥ 16 years actively bleeding and required activation of massive transfusion.	
Length of follow-up	**Outcomes measured**
Databases searched: CENTRAL, DARE and NHSEED, PubMed, MEDLINE, EMBASE, CINAHL (EBSCOHost) and the Transfusion Evidence Library (from inception to 21 February 2017). Ongoing trials searched: ClinicalTrials.gov, WHO International Clinical Trial Registry Platform, and ISCTRN (from inception to 20 April 2017).	Mortality Morbidity Transfusion requirements
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* The main sources of bias risk were lack of blinding of participants and/or clinical and research staff and small sample sizes.	
RESULTS:	
FC versus placebo	

Outcome **No. trials (No. patients)**	**Fibrinogen concentrate** **n/N (%)** **Mean ± SD**	**Placebo** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** ***p*-value (I^2)**
28-day mortality (ITT) n = 45 (1 study) Nascimento 2016	2/21 (9.5)	1/24 (4.2)	RR 2.4 (0.23, 25.0)	NR
ARDS n = 45 (1 study) Nascimento 2016	0/21 (0)	2/24 (8.3)	RR 0.23 (0.01, 4.48)	NR
Multi-organ failure n = 45 (1 study) Nascimento 2016	2/21 (9.5)	2/24 (8.3)	RR 1.14 (0.18, 7.42)	NR
Infection n = 45 (1 study) Nascimento 2016	5/21 (23.8)	8/24 (33.3)	RR 0.71 (0.28, 1.85)	NR
Myocardial infarction n = 45	0	0	Not estimable	NR

(1 study) Nascimento 2016				
Stroke n = 45 (1 study) Nascimento 2016	0	0	Not estimable	NR
Pulmonary embolus n = 45 (1 study) Nascimento 2016	2/21 (9.5)	1/24 (4.2)	RR 2.3 (0.2, 23.4)	NR
Symptomatic deep vein thrombosis n = 45 (1 study) Nascimento 2016	0	0	Not estimable	NR
Deep vein thrombosis on leg doppler n = 29 (1 study) Nascimento 2016	2/15 (13.3)	3/14 (21.4)	RR 0.62 (-0.1, 3.2)	NR
Acute kidney injury n = 45 (1 study) Nascimento 2016	3/21 (14.3)	2/24 (8.3)	RR 1.71 (0.32, 9.3)	NR
RBC transfusion volume, units to 24 hours n = 45 (1 study) Nascimento 2016	Median (IQR) (n = 21) 3 (2–5)	Median (IQR) (n = 24) 3 (2–4)	Not estimable	No significant difference *p* = 0.41
FFP transfusion volume, units to 24 hours n = 45 (1 study) Nascimento 2016	Median (IQR) (n = 21) 2.73 (2.4–3.6)	Median (IQR) (n = 24) 1.75 (1.4–2.0)	Not estimable	No significant difference *p* = 0.72
PLT transfusion volume, units to 24 hours n = 45 (1 study) Nascimento 2016	Median (IQR) (n = 21) 2.81 (2.5–3.6)	Median (IQR) (n = 24) 2.32 (1.9–2.7)	Not estimable	No significant difference *p* = 0.53
CRYO transfusion volume, units to 24 hours n = 45 (1 study) Nascimento 2016	Median (IQR) (n = 21) 4.0 (3.1–4.6)	Median (IQR) (n = 24) 3.5 (2.9–4.0)	Not estimable	No significant difference *p* = 0.18
Cryoprecipitate + standard therapy versus standard therapy				
Mortality 28-day n = 41 (1 study) Curry 2015	2/20 (10)	6/21 (28.6)	RR 0.35 (0.08, 1.54)	No significant difference *p* = 0.14
ARDS	0/20	1/21 (4.8)	RR 0.35 (0.02, 8.10)	NR

n = 41 (1 study) Curry 2015				
Multi-organ failure n = 41 (1 study) Curry 2015	1/20 (5)	0/21	RR 3.14 (0.14, 72.92)	NR
Sepsis n = 41 (1 study) Curry 2015	3/20 (15)	0/21	RR 7.33 (0.40, 133.57)	NR
Myocardial infarction n = 41 (1 study) Curry 2015	0/20	0/21	Not estimable	not estimable
Stroke n = 41 (1 study) Curry 2015	0/20	0/21	Not estimable	not estimable
Pulmonary embolus n = 41 (1 study) Curry 2015	0/20	2/21 (9.5)	RR 0.21 (0.01, 4.11)	NR
Deep vein thrombosis n = 41 (1 study) Curry 2015	0/20	1/21 (4.8)	RR 0.35 (0.02, 8.10)	NR
ICU days n = 41 (1 study) Curry 2015	Median (IQR) 11 (5-17)	Median (IQR) 18 (16-10)	Not estimable	No significant difference *p* = 0.56
In-patient days n = 41 (1 study) Curry 2015	Median (IQR) 31 (29-33)	Median (IQR) 30 (22-38)	Not estimable	No significant difference *p* = 0.66
RBC in 6 hours, units n = 41 (1 study) Curry 2015	Median (IQR) 7 (4-10)	Median (IQR) 7 (4-8)	Not estimable	No significant difference *p* = 0.49
RBC transfusion volume, units, to 24 hours n = 41 (1 study) Curry 2015	Median (IQR) 8 (5-11)	Median (IQR) 7 (6-9)	Not estimable	No significant difference *p* = 0.83
RBC transfusion volume, units, to 28 days n = 41 (1 study) Curry 2015	Median (IQR) 9 (7-15)	Median (IQR) 8 (7-11)	Not estimable	No significant difference *p* = 0.10

FFP transfusion volume, units, to 6 hours n = 41 (1 study) Curry 2015	Median (IQR) 7 (4-8)	Median (IQR) 5 (3-8)	Not estimable	No significant difference *p* = 0.31
FFP transfusion volume, units, to 24 hours n = 41 (1 study) Curry 2015	Median (IQR) 7 (4-8)	Median (IQR) 6 (3-8)	Not estimable	No significant difference *p* = 0.36
FFP transfusion volume, units, to 28 days n = 41 (1 study) Curry 2015	Median (IQR) 8 (4-12)	Median (IQR) 5 (3-8)	Not estimable	No significant difference *p* = 0.06
PLT transfusion volume, units, to 6 hours n = 41 (1 study) Curry 2015	Median (IQR) 1 (0-1)	Median (IQR) 1 (0-1)	Not estimable	No significant difference *p* = 0.89
PLT transfusion volume, units, to 24 hours n = 41 (1 study) Curry 2015	Median (IQR) 1 (0-2)	Median (IQR) 1 (1-2)	Not estimable	No significant difference *p* = 0.56
PLT transfusion volume, units, to 28 days n = 41 (1 study) Curry 2015	Median (IQR) 1 (0-2)	Median (IQR) 1 (1-2)	Not estimable	No significant difference *p* = 0.82
Cryoprecipitate transfusion volume, units to 6 hours n = 41 (1 study) Curry 2015	Median (IQR) 2 (2-4)	Median (IQR) 2 (0-2)	Not estimable	*Favours intervention* *p* = 0.03
Cryoprecipitate transfusion volume, units to 24 hours n = 41 (1 study) Curry 2015	(n = 20) 2 (2-4)	(n = 21) 2 (0-2)	Not estimable	No significant difference *p* = 0.23
Cryoprecipitate transfusion volume, units to 28 days, median (IQR) n = 41 (1 study) Curry 2015	(n = 20) 2 (2-4)	(n = 21) 2 (0-2)	Not estimable	No significant difference *p* = 0.06
Time to first CRYO, minutes n = 41 (1 study)	Median (IQR) 60 (57-76)	Median (IQR) 108 (67-147)	Not estimable	*Favours intervention* *p* = 0.002

Curry 2015				

EXTERNAL VALIDITY

Generalisability (relevance of the study population to the Guidelines target population)

The study population in the systematic review is consistent with the Guideline's target population, i.e., patients who had critical bleeding and had received (or was anticipated to receive) a massive transfusion.

Applicability (relevance of the evidence to the Australian health care system)

Nascimento (2016) was conducted in a single trauma centre in Canada. Curry (2015) was conducted in two major civilian trauma centres in the UK. These studies are directly applicable to the Australian health care system.

Additional comments

Author's conclusions:

Overall, there was moderate quality of evidence for morbidity outcomes and low-quality evidence for mortality comparing RBC to FFP +/−platelet component therapy. There was low-quality evidence for mortality and other outcomes for the other interventions (early CRYO, early fibrinogen concentrate and whole blood).

List of relevant included studies:

Nascimento 2016, Curry 2015

ARDS, acute respiratory distress syndrome; CI, confidence interval; FFP, fresh frozen plasma; h, hours; ICU, intensive care unit; IQR, interquartile range; ITT, intention to treat; IV, intravenous; MD, mean difference; NR, not reported; PICO, population intervention comparator outcome; PLT, platelet; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TXA, tranexamic acid; UK, United Kingdom

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Coccolini 2019

Citation

Coccolini F, Pizzilli G, Corbella D, Sartelli M, Agnoletti V, Agostini V, Baiocchi G.L, Ansaloni L, Catena F. Pre-hospital plasma in haemorrhagic shock management: current opinion and meta-analysis of randomised trials. World Journal of Emergency Surgery (2019) 14:6.

Affiliation/Source of funds

Conflicts of interest: The authors declared no conflicts of interest.

Funding: The authors declared no funding.

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Study design	Level of evidence	Location	Setting
SR and MA of 2 RCTs	I	Moore 2018: US* Sperry 2018: US* *sourced from primary study	Trauma

Intervention	Comparator
Moore 2018: 2 U FFP (approximately 250 mL each) Sperry 2018: 2 U FFP (approximately 250 mL each)	Moore 2018: Standard resuscitation protocol according to the local rules. Sperry 2018: Standard resuscitation protocol according to the local rules.

Population characteristics

In both studies, inclusion criteria were similar and the eligible patients were severely injured adults (age > 18and < 90 years), with SBP 70mmHg or lower or 71–90 mmHg and hearth rate 108 beats per min thought to be due to acute blood loss, either before the arrival of air medical transport or anytime before arrival at the trauma centre.

Length of follow-up	Outcomes measured
Databases searched: MEDLINE, PubMed, CCTR, CDSR, and CINAHL (from inception to August 2018).	Mortality at 24 h and 1 month Acute lung injury Multi-organ failure

STUDY DETAILS: Coccolini 2019				
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. *Risk of bias of included studies:* There is a potential risk of overestimating the beneficial treatment effects of RCT with a resultant risk of bias. The available evidence relies on two out-standing, large, low-biased, RCTs. However, other meta-analyses in the literature have been done with two trials.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**FFP** **n/N (%)** **Mean ± SD**	**SoC** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
2 U FFP vs standard care				
Mortality to 24 hours N = 626 (2 studies) Moore 2018 Sperry 2018	40/295 (13.6) 8/65 (12.3) 32/230 (13.9)	66/331 (19.9) 6/60 (10) 60/271 (22.1)	RR 0.69 (0.48, 0.99) RR 1.23 (0.45, 3.34) RR 0.63 (0.42, 0.93)	*Favours intervention* *p* = 0.04 Minimal heterogeneity I^2 = 34% (*p* = 0.22)
Mortality at 1 month N = 626 (2 studies) Moore 2018 Sperry 2018	78/295 (26.4) 10/65 (15.4) 68/230 (29.6)	104/331 (31.4) 6/60 (10) 98/271 (36.3)	RR 0.86 (0.68, 1.11) RR 1.54 (0.60, 3.98) RR 0.82 (0.63, 1.05)	No significant difference *p* = 0.24 Minimal heterogeneity I^2 = 38% (*p* = 0.21)
Acute lung injury N = 626 (2 studies) Moore 2018 Sperry 2018	76/295 (25.8) 28/65 (43.1) 48/230 (20.9)	80/331 (24.2) 30/60 (50) 50/271 (18.5)	OR 1.03 (0.71, 1.50) OR 0.76 (0.37, 1.53) OR 1.17 (0.75, 1.81)	No significant difference *p* = 0.87 Minimal heterogeneity I^2 = 3% (*p* = 0.31)
Multi-organ failure N = 626 (2 studies) Moore 2018 Sperry 2018	149/295 (50.5) 4/65 (6.2) 145/230 (63.0)	157/331 (47.4) 1/60 (1.7) 156/271 (57.6)	OR 1.30 (0.92, 1.86) OR 3.87 (0.42, 35.63) OR 1.26 (0.88, 1.80)	No significant difference *p* = 0.14 No significant heterogeneity I^2 = 0% (*p* = 0.33)
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats				
Additional comments				
Authors conclusions: The authors concluded that pre-hospital plasma infusion seems to reduce 24 h mortality in haemorrhagic shock patients, however it does not seem to influence 1 month mortality and acute lung injury and multi-organ failure. *List of included relevant trials:* Moore 2018, Sperry 2018				

CI, confidence interval; FFP, fresh frozen plasma; MA, meta-analyses; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk; SBP, systolic blood pressure; SD, standard deviation; SR, systematic review; U, unit; US, United States of America

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Rijnhout 2019			
Citation			
Rjinhout T.W.H, Wever K.E, Marinous R.H.A.R, Hoogerwerf N, Geeraedts Jr L.M.G, Tan E.C.T.H. Is prehospital blood transfusion effective and sae in haemorrhagic trauma patients? A systematic review and meta-analysis. Injury, Int. J. Care Injured 50 (2019) 1017-1027.			
Affiliation/Source of funds			
Conflicts of interest: The authors declared no conflicts of interest. *Funding:* No funding was utilised for this review *Author affiliations:* TWH affiliated with Department of Surgery section Trauma surgery, Radboud University Medical Center, Nijmegen, the Netherlands. KEW affiliated with Systematic Review Center for Laboratory animal Experimentation, department for Health Evidence, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands. RHARM affiliated with Rijks University Groningen, Groningen, the Netherlands. NH affiliated with Department of Anesthesiology and Helicopter Emergency Medical Service Nijmegen lifeliner 3, Radboud university medical center, Nijmegen, the Netherlands. LMGG affiliated with Department of Surgery-section Trauma surgery Amsterdam UMC (previous VUmc), Amsterdam, the Netherlands. ECTHT affiliated with Department of Surgery–Trauma surgery, Radboud University Medical Center, Nijmegen, the Netherlands and Helicopter Emergency Medical Service Nijmegen lifeliner 3, the Netherlands			
Study design	**Level of evidence**	**Location**	**Setting**
Baseline characteristics summarised for 49 studies, including 2 RCTs, 5 case reports, 24 case series and 18 cohort studies. Systematic Review and meta-analysis of 2 RCT and 7 cohort studies	I-III	In total, studies were performed in the US (25), Afghanistan (6), Israel (4), UK (4), Australia (3), the Netherlands (2), Austria (2), Iraq (1), Norway (1) and France (1). Meta analysis was performed in 9 studies: US (5), Afghanistan (2), the Netherlands (1) and UK (1). Studies relevant to PICO: Moore 2018: US Sperry 2018: US Shackelford 2017: Afghanistan Holcomb 2017: US O'Reilly 2014: Afghanistan	Trauma
Intervention		**Comparator**	
Moore 2018: 4 U FFP (37% of patients), 3 U FFP (31% of patients), Saline 150 (0-300) Sperry: 2 U FFP (89.1% of patients), 1 U FFP (9.1% of patients), no plasma (1.7% of patients), pRBC 42.1% and saline 500 (0-1250) Shackelford 2017: 38 patients received pRBCs, 7 patients received plasma only and 10 patients received pRBCs and plasma Holcomb 2017: Plasma only (24% of patients), pRBCs only (7% of patients) and Plasma with pRBCS (69% of patients) O'Reilly 2014: Median 1 U (0-4) pRBC and median 2 U (0-4) FFP		Moore 2018: Saline 250 (100-500) Sperry 2018: pRBCs 42.1% and Saline 900 (0-1500) Shackelford 2017: Standard care Holcomb 2017: Standard care O'Reilly 2014: Standard care	
Population characteristics			
Moore 2018: Civilian blunt trauma patients with a median New Injury Severity Scores (NISS) of 27.0 (10.0-41.0) in patients receiving intervention, and a median NISS score of 27.0 (11.5-36.0) in patients receiving comparator. Sperry 2018: Civilian blunt and penetrating trauma patients with a median Injury Severity Score (ISS) or 22 (14-33) in patients receiving intervention, and a median ISS score of 21 (12-29) in patients receiving comparator.			

STUDY DETAILS: Rijnhout 2019				
Shackelford 2017: Military trauma patients, 9 patients with gunshot wounds and 46 with wounds from explosives in patients that received intervention, 101 patients with gunshot wounds and 244 patients with wounds from explosives in patients that received comparator. Holcomb 2017: Civilian trauma patients, 9 patients with penetrating injury with a median ISS of 24 (10-24) in patients receiving intervention, 18 patients with penetrating injury with a median ISS score of 22 (10-34) in patients receiving comparator. O'Reilly 2014: 1 patient with blunt trauma, 50 patients with explosive trauma and 46 patients with gunshot wound with a median NISS of 22 (15-33) and median ISS of 16 (9-25) in patients receiving intervention, 3 patients with blunt trauma, 48 patients with explosive trauma and 46 patients with gunshot wound with a median NISS of 21 (14-34) and a median ISS of 16 (9-24.5) in patients receiving comparator.				
Length of follow-up		**Outcomes measured**		
Databases searched: CINAHL, Cochrane, EMBASE, Pubmed (from 1988 to 1 August 2018).		Mortality, 24 h and long-term Adverse events by transfusion		
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating: Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and *may not* provide an accurate and comprehensive summary of the available studies that address the question of interest. *Included studies:* Majority of the literature provided mainly poor-quality evidence and was retrospective. Additionally, there is a lack of uniform guidelines for initiating pre-hospital blood transfusion and the liberal use of crystalloids in both intervention and standard care groups makes it difficult to deter the individual effect of pre-hospital blood transfusion.				
RESULTS:				
Outcome No. patients (No. trials)	**[intervention] n/N (%) Mean ± SD**	**[comparator] n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance* *p*-value Heterogeneity[a] I^2 (*p*-value)**
FFP vs saline				
Mortality to 24 hours N = 125 (1 study) Moore 2018	8/65 (12)	6/60 (10)	OR 1.26 (0.41, 3.88)	No significant difference *p* = 0.68
Mortality long-term N = 125 (1 study) Moore 2018	10/65 (15)	6/60 (10)	OR 1.64 (0.56, 4.82)	No significant difference *p* = 0.37
pRBC + plasma vs standard care				
Mortality to 24 hours N = 495 (2 studies) Shackelford 2017 Holcomb 2017	8/97 (8.2) 3/54 (5.6) 5/43 (11.6)	77/398 (19.3) 67/332 (20.2) 10/66 (15.2)	RR 0.47 (0.17, 1.34) RR 0.28 (0.09, 0.84) RR 0.77 (0.28, 2.09)	No significant difference *p* = 0.16 Moderate heterogeneity I^2 = 48% (*p* = 0.16)
Mortality long-term N = 125 (1 study) O'Reilly 2014 Shackelford 2017 Holcomb 2017 Sperry 2018	62/364 (17.0) 8/97 (8.2) 6/54 (11.1) 8/43 (18.6) 40/170 (23.5	185/698 (26.5) 19/97 (19.6) 76/332 (22.9) 14/66 (21.2) 76/203 (37.4)	OR 0.51 (0.36, 0.71) OR 0.37 (0.15, 0.89) OR 0.42 (0.17, 1.02) OR 0.85 (0.32, 2.24) OR 0.51 (0.33, 0.81)	No significant difference *p* < 0.0001 No significant heterogeneity I^2 = 0% (*p* = 0.62)

STUDY DETAILS: Rijnhout 2019
EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
The evidence is directly generalisable to the Australian population with some caveats. Three of the included studies were performed in civilian populations, however two trials (O'Reilly 2014 and Shackelford 2017) were carried out in military settings.
Applicability (relevance of the evidence to the Australian health care system)
The evidence is directly applicable to the Australian healthcare context with few caveats.
Additional comments
Authors conclusions: Carrying and administering blood components is feasible and safe. Pre-hospital blood transfusion with simultaneous use of both pRBCs and plasma resulted in a reduction in the odds for long-term mortality. However, no hard conclusion could be drawn as most studies contained evidence of low-quality. *List of relevant included studies:* Moore 2018, Sperry 2018, O'Reilly 2014, Holcomb 2017, Shackelford 2017

CI, confidence interval; FFP, fresh frozen plasma; h, hours; ISS, injury severity score; ITT, intention-to-treat; MD, mean difference; NISS, new injury severity score; OR, odds ratio; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; U, unit

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Stabler 2020			
Citation			
Stabler S N, Shari Li S, Karpov A and Vu E N. Use of fibrinogen concentrate for trauma-related bleeding: A systematic-review and meta-analysis. J Trauma Acute Care Surg. 2020. 89: 1212-1224. DOI: 10.1097/TA.0000000000002920			
Affiliation/Source of funds			
Author affiliations: Stabler S N affiliated with the Department of Critical Care and the Department of Pharmacy Services, Surrey Memorial Hospital, Surrey, British Colombia; Shari Li S affiliated with the Department of Emergency Medicine, University of British Columbia, Vancouver, British Columbia, Canada; Karpov A and Vu E N affiliated with the Department of Emergency Medicine and Department of Critical Care, University of British Columbia, Vancouver, British Columbia, Canada. Conflicts of interest: The authors declare no conflicts of interest *Funding:* Not reported			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs (6), observational studies (10) and case series/unmatched observational trials (10).	I-II/IV	UK: Curry 2018 Japan: Yamamoto 2016, Inokuchi 2017, Itagaki 2020 Canada: Nascimento 2016 Iran: Akbari 2018 Brazil: Lucena 2020 Germany: Wafaisade 2013 Austria: Innerhofer 2017, Innerhofer 2013, Schochl 2014, Schlimp 2016, Schlimp 2013 Sweden: Almskog 2020 Italy: Bocci 2019 France: David 2016, Hamada 2020 Multi-country (Europe): Ziegler 2019, Schochl 2011, Nienaber 2011	Trauma
Intervention		**Comparator**	
RCT Curry 2018: 6g FC Nascimento 2016: 6g FC		*RCT* Curry 2018: Placebo Nascimento 2016: Placebo	

STUDY DETAILS: Stabler 2020	
Akbari 2018: 2g FC Lucena 2020: 50 mg/kg FC Ziegler 2019: 50 mg/kg FC *Observational* Wafaisade 2013: FC (dose not reported) Yamamoto 2016: 3g FC (fibrinogen <1.5g/L), 3g FC (based on prehospital assessment) Inokuchi 2017: 3g FC (fibrinogen <1.5g/L or need for MTP)+FFP Itagaki 2020: median 3g FC (< 1 hour) Almskog 2020: median 2g (range 2-3g) FC Bocci 2019: 2-4g FC + TXA Hamada 2020: median 3g (range 3-6g) FC Innerhofer 2017: median 8g (range 5-10g) FC ± PCC Schochl 2011:median 6g (range 3-9g) FC ± PCC Innerhofer 2013: median 4g (range 2-4g) FC ± PCC Nienaber 2011: median 4g (range 2-4g) FC ± PCC Schochl 2014: median 3g (range 3-5g) FC, median 8g (range 5-11g) FC ± PCC Schlimp 2016: 1-4g FC, 5-9g FC, ≥10g FC Schlimp 2013: median 7g (range 5-10g) FC + PCC, median 15g (range 9-17g) FC + PCC + FFP David 2016: median 3g (range 3-3g) FC	Akbari 2018: FFP (30/90) or no coagulation products (30/90) Lucena 2020: no FC Ziegler 2019: Placebo *Observational* Wafaisade 2013: no FC Yamamoto 2016: no FC Inokuchi 2017: FFP Itagaki 2020: no FC or delayed (>1 hour) 3g FC Almskog 2020: no FC Bocci 2019: no FC or TXA Hamada 2020: no FC Innerhofer 2017: FFP Schochl 2011: FFP Innerhofer 2013: FFP + median 4g (range 2-4g) FC ± PCC Nienaber 2011: FFP Schochl 2014: no coagulation factors Schlimp 2016: no FC Schlimp 2013: median 3g (range 2-5g) FC David 2016: no haemostatic therapy
Population characteristics	
Patients older than 16 years of age with trauma-related bleeding/coagulopathy	
Length of follow-up	**Outcomes measured**
Databases searched: Medline, PubMed, EMBASE, Web of Science, Cochrane Database of Systematic Reviews, CENTRAL, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (date limit not reported).	Mortality Transfusion requirements (pRBC, FFP, PLT) Hospital length of stay (LOS) ICU LOS Organ failure Thromboembolic events
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The authors noted that two trials were deemed to be at low risk of bias and two trials had unclear risk of bias. Akbari 2018 was deemed to be at high risk of bias due to consecutive randomisation without allocation concealment, lack of blinding and the personnel responsible for allocation also being responsible for data collection.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**FC** **n/N (%)** **Mean ± SD**	**No FC** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
FC versus No FC				
Mortality N = 575 (4 studies) *RCT*				

STUDY DETAILS: Stabler 2020				
Curry 2018 (n = 48) Akbari 2018 (n = 60) Lucena 2020 (n = 32) *Observational* Schlimp 2016 1-4g 5-9g ≥10g	10/24 (42) 3/30 (10) 5/16 (31.2) 4/97 (4.1) 5/93 (5.4) 8/52 (15.4)	7/24 (29.2) 11/30 (36.7) 3/16 (18.8) 12/193 (6.2)	NR NR NR NR	NR *p* = 0.029 *p* = 0.456 *p* = 0.0533
Mortality, overall, in-hospital N = 717 (2 studies) Schochl 2011 Nienaber 2011	 6/80 (7.5) 3/18 (16.7)	 60/601 (10) 2/18 (11.1)	NR	 No significant difference *p* = 0.69 *p* = 0.50
Mortality, 28 days N = 269 (2 studies) Nascimento 2016 Inokuchi 2017	 2/21 (10) 17/115 (15)	 1/24 (4.2) 6/109 (6)	 NR NR	 NR *p* < 0.05
Mortality, 30 days N = 804 (2 studies) Wafaisade 2013 Almskog 2020	 82/294 (27.9) 23/108 (21.3)	 73/294 (24.8) 11/108 (10.2)	 NR NR	 *p* = 0.4 *p* = 0.859
Mortality, 24 hours N = 491 (2 studies) David 2016 Stabler 2020	 6/56 (11) 7/108 (6.5)	 7/219 (29.2) 1/108 (0.9)	 NR NR	 NR *p* = 0.494
Hospital, LOS, days N = 728 (4 studies) *RCT* Curry 2018 (n = 48) Akbari 2018 (n = 60) Lucena 2020 (n = 32) *Observational* Wafaisade 2013 (n = 588)	 NR Mean 11 (SD 6.1) Median 12 (IQR 10, 22) Mean 34.6 (SD 33.3)	 NR Mean 14.8 (SD 7.6) Median 18.5 (IQR 17, 21) Mean 32.8 (SD 28.4)	 NR NR NR NR	 NR *p* = 0.045 NR *p* = 0.96
ICU LOS, days 3 studies, N = 836 RCT Lucena 2020 (n = 32) Observational Wafaisade 2013 (n = 588) Almskog 2020 (n = 216)	 Median 8 (IQR 5.75-10) Mean 17.2 (SD 17.6) Median 7 (IQR 1-20)	 Median 11 (IQR 8.5-16) Mean 17.3 (SD 17.9) Median 5 (IQR 1-16)	 NR NR NR	 *p* = 0.021 *p* = 0.68 *p* = 0.97
MOF				

STUDY DETAILS: Stabler 2020				
5 studies, N = 957 RCT Curry 2018 (n = 48) Akbari 2018 (n = 60) Nascimento 2016 (n = 45) Observational Wafaisade 2013 (n = 588) Almskog 2020 (n = 216)	 NR 2 (7.6) 2 (9.5) 217 (73.8) 1 (0.9)	 NR 7 (23.3) 2 (8.3) 182 (61.9) 1 (0.9)	 NR NR NR NR NR	 NR *p* = 0.106 NR *p* = 0.002 (Favours no FC) *p* = 1.00
Thromboembolic 5 studies, N = 929 RCT Curry 2018 (n = 48) Nascimento 2016 (n = 45) Lucena 2020 (n = 32) Observational Wafaisade 2013 (n = 588) Almskog 2020 (n = 216)	 3 (12.5) 4 (19) 0 20 (6.8) 5 (4.6)	 2 (8.3) 4 (16.7) 0 10 (3.4) 3 (2.8)	 NR NR NR NR NR	 NR NR NR *p* = 0.06 (Favours no FC) *p* = 0.47
Time to receive FC (minutes) 2 studies, N = 93 RCT Curry 2018 (n = 48) Nascimento 2016 (n = 45)	 Median 37.5 (IQR 31, 43.5) Mean 50 (SD 8)	 Median 40 (IQR 23, 76) Mean 51 (SD 8)	 NR NR	 NR *p* = 0.6
FC + FFP versus FFP alone				
Mortality, 28 days 1 study, N = 224 Observational Inokuchi 2017	 17/109 (15)	 6/115 (6)	 NR	 *p* < 0.05
FFP + FC (±PCC) versus FC alone (±PCC)				
Mortality 1 study, N = 94 RCT Innerhofer 2017	 5/50 (10)	 2/44 (5)	 NR	 *p* = 0.44
ICU LOS, days 1 study, N = 94 RCT Innerhofer 2017	 Median (IQR) 9 (4-22)	 Median (IQR) 10 (4.8-23.3)	 NR	 *p* = 0.65
Hospital LOS, days 1 study, N = 94 RCT Innerhofer 2017	 Median (IQR) 28 (18-28)	 Median (IQR) 27 (16-28)	 NR	 *p* = 0.61
Multiple organ failure 1 study, N = 94 RCT Innerhofer 2017	 25/50 (50)	 29/44 (66)	 NR	 *p* = 0.15
Thromboembolic				

STUDY DETAILS: Stabler 2020				
1 study, N = 94 RCT Innerhofer 2017	7/50 (14)	9/44 (20.5)	NR	NR

EXTERNAL VALIDITY

Generalisability (relevance of the study population to the Guidelines target population)

The evidence is directly generalisable to the Australian population. Studies are carried out in trauma patients which are similar to trauma patients within the Australian population.

Applicability (relevance of the evidence to the Australian health care system)

The evidence is probably applicable to the Australian healthcare context with some caveats. Two RCTs are carried out in healthcare settings similar to Australia. Findings from other RCTs and observational studies that are not carried out in healthcare systems similar to Australia could be sensibly applied to the Australian healthcare context.

Additional comments

Authors conclusions:

There is a paucity of studies assessing the potential impact of FC as a pre-emptive or goal-directed strategy in early, balanced, blood-product–based resuscitation from trauma induced haemorrhage and coagulopathy. Of the randomized data available comparing FC to placebo or standard care, no mortality benefit has been demonstrated, nor any change in transfusion volume. Further adequately powered studies are needed to assess the impact of FC in haemorrhagic shock and TIC, with a focus on administration as early as possible from the point of injury or point of entry into the trauma system of care.

List of relevant included studies:

RCTs Curry 2018, Nascimento 2016, Akbari 2018, Lucena 2020

Observational: Wafaisade 2013, Yamamoto 2016, Inokuchi 2017, Almskog 2020, Hamada 2020, Innerhofer 2017, Schochl 2014, Schlimp 2016, Schlimp 2013, David 2016

CI, confidence interval; FC, fibrinogen concentrate; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MOF, multiple organ failure; NR, not reported; PCC, prothrombin complex concentrate; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TIC, trauma induced coagulopathy; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: van den Brink 2020

Citation

van den Brink D, Wirtz M R, Serpa Neto A, Schochl H, Viersen V, Binnekade J and Juffermans N P. Effectiveness of prothrombin complex concentrate for the treatment of bleeding: A systematic review and meta-analysis. J Thromb Haemost. 2020. 18:2457-2367. DOI: 10.1111/jth.14991

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Conflicts of interest: The authors declare no conflicts of interest

Study design	Level of evidence	Location	Setting
Systematic review and meta-analysis of prospective studies (2) and retrospective studies (15)	I-III	Not reported	Surgical (12), trauma (4) and other (1).

STUDY DETAILS: van den Brink 2020	
Intervention	**Comparator**
Zeeshan 2019: 4-factor PCC +FFP Jehan 2018: 4-factor PCC +FFP Joseph 2016: 3-factor PCC +FFP Joseph 2014: 3-factor PCC +FFP DeLoughery 2016: 4-factor PCC	Zeeshan 2019: FFP Jehan 2018: FFP Joseph 2016: FFP Joseph 2014: FFP DeLoughery 2016: rFVIIa
Population characteristics	
Patients ≥ 18 years of age with active bleeding	
Length of follow-up	**Outcomes measured**
Databases searched: MEDLINE, EMBASE, CINAHL (from 1952 to April 2020).	All-cause mortality Blood loss RBC utilisation Thromboembolic events
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. *Risk of bias of included studies:* The authors noted that the review may be at risk of language bias. Of the 17 included studies, 13 were assessed as having a good quality, one had fair quality and three were rated as having a poor quality.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**PCC** **n/N (%)** **Mean ± SD**	**No PCC** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
PCC versus no PCC				
Mortality N = 921 (4 studies) Jehan 2018 Joseph 2014 Joseph 2016 Zeeshan 2019	72/364 (19.8) 10/40 (25) 15/63 (23.8) 6/27 (22.2) 41/234 (17.5)	159/557 (28.5) 26/80 (32.5) 53/189 (28.0) 15/54 (27.8) 65/234 (27.8)	OR 0.64 (0.46, 0.88) OR 0.69 (0.29, 1.63) OR 0.80 (0.41, 1.55) OR 0.74 (0.25, 2.20) OR 0.55 (0.35, 0.86)	*Favours PCC* *p* = 0.007 No heterogeneity I^2 = 0% (*p* = 0.81)
RBC utilisation, units N = 921 (4 studies) Jehan 2018 Joseph 2014 Joseph 2016 Zeeshan 2019	N = 364 7±3 (n = 40) 6.6±4.1 (n = 63) 3.2±1.9 (n = 27) 6±4 (n = 234)	N = 557 9±5 (n = 80) 10±8.3 (n = 189) 5.4±4.1 (n = 54) 10±4 (n = 234)	MD -2.99 (-4.06, -1.91) MD -2.00 (-2.44, -0.56) MD -3.40 (-4.96, -1.84) MD -2.20 (-3.51, -0.89) MD -4.00 (-4.72, -3.28)	*Favours PCC* *p* < 0.00001 Significant heterogeneity I^2 = 68% (*p* < 0.0001)
Thromboembolic events N = 921 (4 studies) Jehan 2018 Joseph 2014 Joseph 2016 Zeeshan 2019	18/364 (4.9) 1/40 (2.5) 2/63 (3.2) 4/27 (14.8) 11/234 (4.7)	27/557 (4.8) 2/80 (2.5) 3/189 (1.6) 5/54 (9.3) 17/234 (7.3)	OR 0.90 (0.49, 1.67) OR 1.00 (0.09, 11.37) OR 2.03 (0.33, 12.45) OR 1.70 (0.42, 6.95) OR 0.63 (0.29, 1.38)	No significant difference *p* = 0.74 No heterogeneity I^2 = 0% (*p* < 0.50)

STUDY DETAILS: van den Brink 2020
EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
The evidence is not directly generalisable to the Australian population but could be sensibly applied. Populations include trauma and cardiothoracic patients. Despite limited population descriptions and potential heterogeneity across populations, this could be sensibly applied to the Australian population.
Applicability (relevance of the evidence to the Australian health care system)
The evidence is probably applicable to the Australian healthcare context with some caveats. The authors did not report on the location of each study.
Additional comments
Authors conclusions: PCC administration in bleeding patients not using anticoagulants had no effect on mortality in the whole cohort of patients. However, in trauma patients, a resuscitation strategy using both PCC and FFP transfusion was associated with reduced mortality when compared to a resuscitation strategy involving solely FFP. Also, PCC reduced the need for RBC transfusions when compared with treatment strategies not involving PCC. In bleeding cardiac surgery patients, PCC administration reduced perioperative blood loss. Risk of TE events were not increased. However, results are subject to considerable heterogeneity and should be interpreted with caution. These data, derived from observational studies, can be used to design trials to further explore the effectivity of PCC in different clinical scenarios of bleeding. *List of relevant included studies:* Zeeshan 2019, Jehan 2018, Joseph 2016, Joseph 2014, DeLoughery 2016

CI, confidence interval; FFP, fresh frozen plasma; MD, mean difference; OR, odds ratio; PCC, prothrombin complex concentrate; RBC, red blood cell; rFIIA, recombinant factor VII; SD, standard deviation; TE, thromboembolic event

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Zaidi 2020			
Citation			
Zaidi A, Kohli R, Daru J, Estcourt L, Khan K S, Thangaratinam S, Green L. Early Use of Fibrinogen Replacement Therapy in Postpartum Hemorrhage-A Systematic Review. 2020. 34:101-107.			
Affiliation/Source of funds			
Funding: The study was funded by Barts Charity. The funders had no role in the Study design, data collection, analysis or preparation of this article. The views expressed in this article are those of the authors and not necessarily of the funders. *Affiliations:* Zaidi A, Daru J, Khan K S and Shakila T affiliated with Barts Research Centre for Women's Health, Queen Mary University of London, UK Zaidi A, Kohli R, Thangaratinam S and Green L affiliated with Barts Health, NHS Trust, London, UK Kohli R affiliated with Wolfson Institute, Queen Mary University of London, UK Estcourt L and Green L affiliated with NHS Blood and Transplant, UK, Radcliffe Department of Medicine, University of Oxford, UK and Blizzard Institute, Queen Mary University of London, UK. *Conflicts of interest:* Green L, Thangaratinam S, Daru J, and Khan K S are investigators of the ongoing ACROBAT trial reported in this review. Daru J has received fees from Pharmacosmos for advisory work.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of RCTs (5)	I	Wikkelso 2015: Denmark Collins 2017: Not reported	Obstetrics
Intervention		**Comparator**	
Wikkelsø 2015: 2g FC Collins 2017: 1g FC guided by viscoelastic testing		Wikkelsø 2015: 100 mL normal saline Collins 2017: 50 mL normal saline	
Population characteristics			
Wikkelsø 2015: Women with PPH, Caesarean section with an estimated perioperative blood loss > 1L or vaginal delivery with either estimated blood loss > 0.5L and intended manual removal of placenta or estimated blood loss > 1L and intended manual exploration of the uterus because of continuous bleeding after delivery of the placenta. Collins 2017: Only women with ongoing major PPH were screened with ROTEM			

STUDY DETAILS: Zaidi 2020	
Length of follow-up	**Outcomes measured**
Databases searched: CDSR and CENTRAL, MEDLINE, Embase, CINAHL, PubMed, Transfusion Evidence Library, LILACS, Web of Science Conference Proceedings Citation Index-Science, ClinicalTrials.gov and the WHO International Clinical Trials Registry Portal (from inception to June 2019).	Transfusion requirements Mortality, 24 hours, 7 days and 30 days Thrombosis ICU length of stay Hospital length of stay
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. *Risk of bias of included studies:* Collins 2017 was classified as having an overall low risk of bias. The authors acknowledged that Collins 2017 was funded by CSL Behring, which is the manufacturer of the fibrinogen concentrate. Wikkelsø 2015 was rated to have an unclear risk of bias. The main sources of bias in Wikkelsø 2015 were attrition bias due to incomplete outcome data reporting.	
RESULTS:	

Outcome **No. patients** **(No. trials)**	**FC** **n/N (%)** **Mean ± SD**	**No FC** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
FC versus no FC				
Need for RBC transfusion < 6 weeks post PPH N = 244 (1 study) Wikkelsø 2015	25/123 (20.3)	26/121 (21.5)	NR	No significant difference *p* = 0.88
Transfusion requirement, units at 7 days N = 55 (1 study) Collins 2017	2.07	2.78	Adjusted rate ratio 0.72 (0.30, 1.70)	No significant difference *p* = 0.45
Mortality, 30 days N = 299 (2 studies) Collins 2017 Wikkelsø 2015	0/151 0/28 0/123	0/148 0/27 0/121	NR	*p* = NR
Thrombosis up to 6 weeks N = 55 (1 study) Collins 2017	1/28 (3.6)	1/27 (3.7)	NR	NR
Length of hospital stay, median days (IQR) N = 55 (1 study) Collins 2017	3 (2-5)	3 (2-4)	NR	No significant difference *p* = 0.13
Length of ICU stay, median days (IQR) N = 55	16 (12-25)	20.5 (10.5-28.5)	Difference 0.90	NR

STUDY DETAILS: Zaidi 2020				
(1 study) Collins 2017				
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. The studies were conducted in women with PPH including women with and without Caesarean sections and is representative of the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats. The authors reported on the location of one study in Denmark which has a similar healthcare system to Australia.				
Additional comments				
Authors conclusions: This review has demonstrated the paucity of evidence on the early use of fibrinogen replacement therapies in postpartum haemorrhage. The small sample size of included studies and their heterogeneity warrants us to interpret these results with extreme caution until further evidence become available. Therefore, future trials are urgently needed to assess the clinical efficacy and safety of early fibrinogen replacement therapy (particularly CRYO) in PPH. Evidence is required to determine the optimal dose of fibrinogen replacement therapy in PHH as well as compare the cost-effectiveness of CRYO transfusion with fibrinogen concentrate, and protocol-driven approaches with targeted-therapy for fibrinogen replacement therapy. *List of relevant included studies:* Wikkelso 2015, Collins 2017				

CI, confidence interval FC, fibrinogen concentrate; ICU, intensive care unit; IQR, inter quartile range; NR, not reported; PPH, postpartum haemorrhage; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

Randomised controlled trials

No additional studies identified.

Observational / cohort studies

STUDY DETAILS: Inokuchi 2017			
Citation			
Inokuchi, K., Sawano, M., Yamamoto, K., Yamaguchi, A., & Sugiyama, S. (2017). Early administration of fibrinogen concentrates improves the short-term outcomes of severe pelvic fracture patients. Acute medicine & surgery, 4(3), 271–277. doi:10.1002/ams2.268			
Affiliation/Source of funds			
Conflicts of interest: The authors declared no conflicts of interest. *Funding:* Details on funding not provided. *Author affiliations:* KI, MS, AY and SS affiliated with Department of Emergency and Critical Care Medicine, Saitama Medical Center, Saitama Medical University. KY affiliated with Department of Transfusion Medicine and Cell Therapy, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan.			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort study	III-3	Saitama, Japan	Single centre, trauma
Intervention		**Comparator**	
Group L (n = 109) Revision of massive transfusion protocol (MTP, described in Figure 1) to include early off-label admiration of 3g fibrinogen concentrate (FC) FC administered if plasma fibrinogen levels were below 150 mg/dL – April 2013 to March 2014 FC administered when MTP activated from April 2014 to March 2015		Group E (n = 115) MTP prior to revision without FC	
Population characteristics			
Patients with pelvic fractures from blunt trauma requiring activation of MTP			
Length of follow-up		**Outcomes measured**	
Enrolled eligible patients hospitalised from January 2011 to March 2015 Missing data for physical status on admission: 13/115 in Group E and 11/109 in Group L Missing data for haematological status on admission: 14/115 in Group E and 12/109 in Group L		28-day mortality Number of blood transfusions within 7 days of admission Implementation of interventions including trans-arterial embolisation (TAE), injury to TAE, admissions to TAE, external fixation, internal fixation and pelvic packing	
Method of analysis			
The χ2-test was used for evaluation of intergroup differences in sex, hospitalisation routes, medications, allo-type packed red blood cells transfusion, and implementation of the interventions. Mann–Whitney's U-test was used for others. The significance level was 5% ($p < 0.05$). Impacts of the revision and the characteristics, injury severity, and coagulation status on 28-day survival were evaluated using Cox's multivariate proportional hazard model. The groups (the revision), age, sex, interval between injury and admission, Injury Severity Score, Revised Trauma Score, and blood haemoglobin concentration, prothrombin time – international normalized ratio, activated partial thrombin time, serum fibrinogen concentration, and platelet count on admission were assigned to the model as explanatory covariates, and 28-day mortality as the objective variate. Their impact on survival was evaluated in terms of hazard ratios adjusted for other covariates. Impact of the revision on the outcome was also evaluated by the univariate log–rank test between the survival curves, and relative risk of 28-day mortality between the groups.			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has some important problems and cannot be considered comparable to a well-performed randomised trial.			

STUDY DETAILS: Inokuchi 2017				
Limitations were missing data and the substantial change in threshold and timing for administration of FC to the patients in Group L during the study period. Another major limitation derives from the absence of a clear objective criterion for activation of MTP throughout the study period. The activation was left to the clinical decision, and its consistency among the groups was not guaranteed. In the same context, consistency for the implementation of surgical or radiological interventions was not guaranteed. The possible bias in the activation of MTP and the implementation of interventions may influence the discrepancy of the survival between the groups.				
RESULTS				
Population analysed	**Comparator**		**Intervention**	
Available	115		109	
Analysed	115		109	
Outcome	**Comparator n/N (%) Mean ± SD**	**Intervention n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
Group E (pre revision) vs Group L (post revision)				
28-day mortality All ISS ISS ≥ 21	17/115 (15)	6/109 (6)	 RR 0.37 (0.15, 0.91) RR 0.33 (0.13, 0.84)	*Favours revision* *p* = 0.022 *p* = 0.009
Number of blood transfusion within 7 days of admission - packed RBCs, units	Median (IQR) 10 (4, 22)	Median (IQR) 10 (6, 20)	NR	No significant difference *p* = 0.958
- packed RBCs ≥ 1 unit	78/115 (67.8)	68/109 (62.4)	NR	No significant difference *p* = 0.409
- packed RBCs ≥ 6 units	55/115 (47.8)	54/109 (49.5)	NR	No significant difference *p* = 0.297
- allo-type packed RBCs	2/115 (1.7)	3/109 (2.8)	NR	No significant difference *p* = 1.000
- fresh frozen plasma, units	Median (IQR) 10 (6, 20)	Median (IQR) 8 (6, 20)	NR	No significant difference *p* = 0.685
- platelet concentrate, units	20 (20, 37.5) Median IQR)	20 (20, 20) Median (IQR)	NR	No significant difference *p* = 0.251
Trans-arterial embolisation	36/115 (31)	28/109 (26)	NR	No significant difference *p* = 0.764
Interval between injury and completion of TAE, minutes	Median (IQR) 184 (156, 220)	Median (IQR) 178 (146, 211)	NR	No significant difference *p* = 0.386
Interval between admission and completion of TAE, minutes	Median (IQR) 114 (88.5, 128)	Median (IQR) 95 (66, 124)	NR	No significant difference *p* = 0.279
External fixation	13/115 (11)	14/109 (13)	NR	No significant difference *p* = 0.838
Internal fixation	42/115 (36)	43/109 (39)	NR	No significant difference *p* = 0.681
Pelvic packing	3/115 (3)	2/109 (2)	NR	No significant difference *p* = 1.000

STUDY DETAILS: Inokuchi 2017
EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
The evidence is directly generalisable to the Australian population, eligible patients were those with pelvic fractures due to blunt trauma requiring MTP.
Applicability (relevance of the evidence to the Australian health care system)
The evidence is directly applicable to the Australian healthcare context with few caveats, depending on the composition of the MTP.
Additional comments
Author's conclusions: The revision of MTP to include aggressive off-label treatment with fibrinogen concentrate was related to improved short-term outcomes of severe pelvic fracture patients. However, due to the limitations of the study, the improvement could not be attributed totally to the revision.

CI, confidence interval; FC, fibrinogen concentrate; ISS, injury severity score; MTP, massive transfusion protocol; NR, not reported; RBC, red blood cells; SD, standard deviation; TAE, trans-arterial embolization.

E7 Tranexamic acid (Question 7)

Systematic reviews/meta-analyses

STUDY DETAILS: Ausset 2015			
Citation			
Ausset, S., Glassberg, E., Nadler, R., Sunde, G., Cap, A. P., Hoffmann, C., Plang, S. & Sailliol, A. 2015. Tranexamic acid as part of remote damage-control resuscitation in the prehospital setting: A critical appraisal of the medical literature and available alternatives. *Journal of Trauma and Acute Care Surgery*, 78(6), S70-S75. doi: 10.1097/TA.0000000000000640.			
Affiliation/Source of funds			
Details on funding were not provided. The authors declared no conflicts of interest. (pS74) *Author affiliations:* Department of Anesthesiology and Intensive Care (S.A.), Percy Military Hospital; and Centre de Transfusion Sanguine des Arme´es rue Raoul Batany (S.P., A.S.), Clamart; and French Military Health Service Academy-Ecole du Val-de-Gra^ce (C.H.), Paris, France; The Trauma and Combat Medicine Branch (E.G., R.N.), the Surgeon Generals' Headquarters, Israel Defense Forces Medical Corps, Ramat Gan, Israel; Norwegian Air Ambulance Foundation (G.S.), Drøbak, Norway; and Blood Research Program (A.P.C.), US Army Institute of Surgical Research, JBSA-Fort Sam Houston, Texas			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of meta-analyses, retrospective analyses, cohort studies, case control studies and observational studies *only data from studies relevant to the Guidelines are extracted here	I	Apodaca 2013: Norway Benov 2014: Israeli-Syrian border Lipsky 2014: Israel Morrison 2012, Morrison 2013: Afghanistan Vu 2013: Canada Countries of origin for remaining individual studies not provided.	Shakur 2010, Cole 2014, Valle 2014: hospital, trauma Morrison 2012, Morrison 2013: hospital, war surgery Apodaca 2013, Benov 2014, Lipsky 2014, Vu 2013: prehospital
Intervention		**Comparator**	
Shakur 2010: TXA 1 g over 10 min, then 1 g over 8 hrs Lipsky 2014: TXA administered with freeze-dried plasma TXA administered for all remaining individual studies, but no further information provided.		Shakur 2010, Cole 2014, Morrison 2012, Valle 2014: No TXA Morrison 2013: CRYO, TXA and CRYO, no TXA or CRYO	
Population characteristics			
Relevant to this review (trauma setting) *Shakur 2010 (CRASH-2):* RCT in trauma patients, wide range of injury severities, most enrolled in low-income countries *Cole 2014:* Prospective cohort study in civilian adult patients with severe trauma, Injury Severity Score (ISS) > 15 (N = 385) *Morrison 2012 (MATTERS):* Retrospective study in war surgery patients receiving ≥ 1 U packed red blood cells *Morrison 2013 (MATTERS II):* Prospective study in war surgery patients, requiring ≥ 1 U packed red blood cells *Valle 2014:* Retrospective case-control study in civilian trauma patients (N = 300) *Relevant, but study type does not meet the PICO criteria for this review* *Apodaca 2013:* Single-arm descriptive study, haemorrhaging aeromedical patients; trauma and non-trauma *Benov 2014:* Single-arm descriptive study, Syrian casualties secondary to Syrian civil war *Lipsky 2014:* Single-arm descriptive study, Israeli Defence Force casualties *Vu 2014:* Single-arm descriptive study, aeromedical evacuation patients *Not relevant to these Guidelines (not trauma)* *Ker 2012:* Meta-analysis of 129 trials involving surgical patients, majority in elective cardiac surgery *Zufferey 2006:* Meta-analysis of 18 trials involving orthopaedic surgery			

STUDY DETAILS: Ausset 2015	
Poeran 2014: Retrospective analysis of orthopaedic patients, undergoing total hip or knee arthroplasty over 6-year period in 510 US hospitals *Berntorp 2001*: Case Control Study in female patients with menorrhagia *Sundström 2009*: Case Control Study in female patients with menorrhagia	
Length of follow-up	**Outcomes measured**
Citations published between Jul 2003 and Dec 2015. No details provided regarding follow up post TXA intervention.	Mortality, blood transfusion, need for surgery, blood products transfused, ISS, incidence of shock, multiorgan failure (MOF), thromboembolic events (VTE, DVT, PE)
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. The authors did not provide any information regarding inclusion criteria, research question/s, Study design selection, search strategy, duplicate study selection and data extraction, excluded studies, funding sources for individual studies, or an investigation of publication bias. The authors did not formally analyse the quality of other included studies. No meta-analysis was performed, and information regarding individual study populations, interventions, comparators and results was often insufficient and/or inconsistent. *Risk of bias of included studies:* Key issues with Shakur 2010 included reporting bias (no systematic adverse event reporting, making it difficult to interpret results relating to thrombotic risk, and reporting of blood loss and injury severity), and potential for confounding and measurement error (few patients came from countries with early access to blood products or availability of state-of-the-art trauma care) . There were issues with a confounding effect of heterogeneous rFVIIa use in for Morrison 2013 and limitations of a retrospective Study design suggested for Morrison 2012, in addition to potential confounding factor of increased CRYO use for the TXA group (noting that this confounding factor was accounted for in the follow up study, Morrison 2013). Potential selection bias and a lack of multivariate analysis were identified as important flaws in Valle 2014. Confounding was also identified in Lipsky 2014 with regards to an association with thromboembolic events. The authors also admit that, due to the setting of this and other pre-hospital studies, longer term complications of TXA administration could not be assessed.	
RESULTS:	

Outcome **No. patients** **(No. trials)**	**TXA** **n/N (%)** **Mean ± SD**	**No TXA** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
TXA versus no TXA (trauma setting)				
Mortality, overall N = 23 124 (1 RCT, 4 Coh) Shakur 2010 Morrison 2012 Morrison 2013 Valle 2014 Cole 2014	 NR (14.5%) NR/293 (17.4%) NR NR/150 NR/160 (8%)	 NR (16%) NR/603 (23.9%) NR NR/150 NR/225 (8%)	 ARR 0.015 NR OR 0.61 (0.42, 0.89) NR NR	Meta-analysis not performed NR, Favours TXA [b] NR, Not significant [c] NR, Favours TXA [d] NR, Not significant [e] NR, Not significant [f]
Mortality, subgroups N = NR (2 Coh) Morrison 2012 patients requiring a massive transfusion Cole 2014 patients with shock	 NR (14.4%)	 NR (28.1%)	 OR 7.2 (3.0, 17.3) OR 0.16 (0.31, 0.86)	 NR, Favours TXA NR, Favours TXA [f]
Vaso-occlusive events, overall N = 20211 (1 RCT)	NR (1.7%)	NR (2.0%)	NR	No significant difference NR Heterogeneity NA

STUDY DETAILS: Ausset 2015				
Shakur 2010				
Venous thromboembolism N = NR (1 RCT, 1 Coh) Shakur 2010 Morrison 2012	 NR NR	 NR NR	 NR NR	Meta-analysis not performed NR, Not significant NR, Not significant
Pulmonary embolism N = 20211 (1 RCT) Shakur 2010	NR	NR	NR	No significant difference NR Heterogeneity NA
Stroke N = 20211 (1 RCT) Shakur 2010	NR	NR	NR	No significant difference NR Heterogeneity NA
Myocardial infarction N = 20211 (1 RCT) Shakur 2010	NR	NR	NR	*Favours TXA* NR Heterogeneity NA
Multiorgan failure N = NR (1 Coh) Cole 2014 Patients with shock	NR/160 (30%) NR	NR/225 (37%) NR	NR OR 0.27 (0.1 , 0.73)	No significant difference NR Heterogeneity NA *Favours TXA* [g]
Cryoprecipitate versus no cryoprecipitate				
Mortality N = NR (1 Coh) Morrison 2013	NR	NR	OR 0.61 (0.40, 0.94)	NR, *Favours TXA* [h]
TXA and cryoprecipitate versus no TXA or cryoprecipitate				
Mortality N = NR (1 Coh) Morrison 2013	NR	NR	OR 0.34 (0.20, 0.58)	NR, *Favours TXA* [i]
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply. The review provides both insufficient and inconsistent data in regard to populations, severity and type of injury and intervention methods. Moreover, Shakur 2010 reportedly involved a population with a wide range of injury severity, while Apodaca 2013 included non-trauma patients. When taking these issues into account, along with the very low INTERNAL VALIDITY of the review, it is difficult to judge the level of relevance to the Guidelines target population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. Three of the studies (Morrison 2012, Morrison 2013 and Benov 2014) occurred in a wartime context. Moreover, Poeran 2014 took place in the USA health care context, which is not comparable to the Australian health care system. Notwithstanding this, three of the studies occurred in health care systems that are comparable to Australia: Vu 2013 (Canada), Apodaca 2013 (Norway) and Lipsky 2014 (Israel). Given the wide variety of health care contexts mentioned above, in addition to the absence of country of origin data for the remaining eight studies, it is difficult to comment on the applicability of these results.				
Additional comments				
Authors conclusions: There are no better pharmacologic haemostatic interventions than TXA in the prehospital context.				

STUDY DETAILS: Ausset 2015
That there was high quality evidence favouring use of TXA to reduce bleeding in elective surgery, and to decrease mortality in trauma patients. However, they contended that this mortality reduction had occurred over a wide range of injury severities in the included studies. They also suggested that TXA administration within the first hour post-injury was most effective, with prehospital intervention being the best way to ensure this occurred. Notwithstanding this, they admitted that data involving prehospital TXA use was limited. Evidence showed that there was a low risk of adverse effects. Despite the above conclusions, the authors acknowledged that ongoing research into TXA use in trauma settings was needed, including more exploration into associations with adverse thrombotic events. They also suggested that TXA use in the prehospital setting should be considered in combination with transfusion of blood products such as freeze-dried plasma, RBCs and fibrinogen. *List of included studies* Shakur 2010, Cole 2014, Morrison 2012, Morrison 2013, Valle 2014

CI, confidence interval; Coh, cohort; ITT, intention-to-treat; MD, mean difference; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TBI, traumatic brain injury; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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%.

b. Ausset 2015 noted that a post-hoc analysis had revealed when TXA was administered within 1 hour after trauma, mortality was reduced by one-third. Between hours 1–3, mortality was reduced by one-fifth. When given after the third hour, mortality due to bleeding appeared to increase.

c. Ausset 2015 noted that the survival benefit of TXA in Morrison 2012 was confounded by the retrospective Study design, with CRYO used more often in the TXA massive transfusion group. Factors significantly associated with death in the entire cohort included: Glasgow Coma Score of 8 or less, hypotension, and coagulopathy.

d. Propensity score adjusted for predictors of mortality, including RBCs, FFP, and plasma. After adjustment for platelet administration the OR was 0.62 (95% CI 0.43, 0.90). Ausset 2015 noted that the survival benefit of TXA in Morrison 2013 remained confounded by the heterogeneous use of rFVIIa.

e. Ausset 2015 noted that mortality was higher in the TXA group, but that the study by Valle (2014) was confounded by the propensity score failing to account for important variables, resulting in the TXA group being more severely injured than the control group. No multivariate analysis was performed to account for these differences.

f. The survival benefit of TXA in Cole 2014 is confounded. Patients who received TXA had higher ISS, incidence of shock (base deficit > 6 mEq/L) and transfusion requirements. A multivariate analysis in the subgroup of patients with shock revealed an effect favouring TXA OR 0.16 (0.31, 0.86).

g. The benefit of TXA in Cole 2014 is confounded. Patients who received TXA had higher ISS, incidence of shock (base deficit > 6 mEq/L) and transfusion requirements. A multivariate analysis in the subgroup of patients with shock revealed an effect favouring TXA OR 0.27 (0.1, 0.7).

h. Propensity score adjusted for predictors of mortality, including RBCs, FFP, and plasma. After adjustment for platelet administration the OR was 0.62 (95% CI 0.39, 0.91). Ausset 2015 noted that the survival benefit of TXA in Morrison 2013 remained confounded by the heterogeneous use of rFVIIa.

i. Propensity score adjusted for predictors of mortality, including RBCs, FFP, and plasma. After adjustment for platelet administration the OR was unchanged. Ausset 2015 noted that the survival benefit of TXA in Morrison 2013 remained confounded by the heterogeneous use of rFVIIa.

STUDY DETAILS: Ker 2015			
Citation			
Ker, K., Roberts, I., Shakur, H., et al. 2015. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database of Systematic Reviews*, CD004896.			
Affiliation/Source of funds			
The Cochrane Review project was supported by the National Institute for Health Research, UK, through Cochrane Infrastructure funding to the Cochrane Injuries Group. All authors declared an interest in clinical trials assessing TXA (including those for postpartum haemorrhage, acute traumatic brain injury, GI bleeding, and trauma)			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic Review of RCTs	Level I	*CRASH-2 2010:* 40 countries not specified *Yutthakasemsunt 2013:* Thailand *McMichan 1982:* Australia	Trauma (in-hospital)
Intervention		**Comparator**	
Aprotinin or tranexamic acid (TXA)		Placebo	

STUDY DETAILS: Ker 2015				
CRASH-2 2010: 1 g TXA loading dose over 10 minutes followed by infusion of 1g over 8 hours *Yutthakasemsunt 2013:* 1 g TXA loading dose over 30 minutes followed by infusion of 1g over 8 hours *McMichan 1982:* 500 KIU aprotinin followed by 300,000 IV every six hours for 96 hours				
Population characteristics				
People of any age following acute traumatic injury. *CRASH-2 2010:* Adult trauma patients with, or at risk of, significant bleeding. Includes 270 patients who also had TBI (substudy). *Yutthakasemsunt 2013:* Adults patients with moderate to severe traumatic brain injury *McMichan 1982:* Patients with a combination of hypovolaemic shock and major fractures of the lower limb and or pelvis.				
Length of follow-up	**Outcomes measured**			
Follow-up generally not specified, but usually period of hospitalisation	*All trauma:* All-cause mortality, Morbidity (deep vein thrombosis, pulmonary embolism), Volume of blood transfused *TBI patients:* All-cause mortality, Morbidity (deep vein thrombosis, pulmonary embolism)			
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. The authors planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis. Authors only stated conflict of interest and declared funding source for the systematic review.				
RESULTS:				
Outcome **No. patients (No. trials)**	**TXA** **n/N (%)** **Mean ± SD (n)**	**No TXA** **n/N (%)** **Mean ± SD (n)**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** **I^2 (*p*-value)**
TXA versus placebo				
Mortality, all cause All trauma N = 20367 (2 trials) CRASH-2 2010 Yutthakasemsunt 2013	1475/10180 1463/10060 12/120	1631/10187 1613/10067 18/120	RR 0.90 (0.85, 0.97) 0.91 (0.85, 0.97) 0.67 (0.34, 1.32)	*Favours TXA* p = 0.003 No significant heterogeneity I^2 = 0% (p = 0.38)
Mortality, all cause TBI subgroup N = 510 (2 trials) CRASH-2 2010 Yutthakasemsunt 2013	26/253 14/133 12/120	42/257 24/137 18/120	RR 0.63 (0.40, 0.99) 0.60 (0.33, 1.11) 0.67 (0.34, 1.32)	*Favours TXA* *p* = 0.047 No significant heterogeneity I^2 = 0% (*p* = 0.82)
Myocardial infarction All trauma N = 20367 (2 trials) CRASH-2 2010 Yutthakasemsunt 2013	351/10180 35/10060 0/120	58/10187 55/10067 3/120	RR 0.61 (0.40, 0.92) 0.64 (0.42, 0.97) 0.14 (0.01, 2.74)	No significant difference *p* = 0.019 No significant heterogeneity I^2 = 0% (p = 0.32)
Stroke TBI subgroup N = 510 (2 trials) CRASH-2 2010	0/253 0/133	1/257 1/137	RR 0.34 (0.01, 8.35) 0.34 (0.01, 8.35)	No significant difference *p* = 0.51 Heterogeneity NA

STUDY DETAILS: Ker 2015				
Yutthakasemsunt 2013	0/120	0/120	Not estimable	
Deep vein thrombosis All trauma N = 20 367 (2 trials) CRASH-2 2010 Yutthakasemsunt 2013	40/10180 40/10060 0/120	42/10187 41/10067 1/120	RR 0.95 (0.62, 1.47) 0.98 (0.63, 1.51) 0.33 (0.01, 8.10)	No significant difference p = 0.83 No significant heterogeneity I^2 = 0% (p = 0.51)
Deep vein thrombosis TBI subgroup N = 510 (2 trials) CRASH-2 2010 Yutthakasemsunt 2013	0/ 253 0/133 0/120	3/ 257 2/137 1/120	RR 0.25 (0.03, 2.26) 0.21 (0.01, 4.25) 0.33 (0.01, 8.10)	No significant difference p = 0.22 No significant heterogeneity I^2 = 0% (p = 0.83)
Pulmonary embolism All trauma N = 20 367 (2 trials) CRASH-2 2010 Yutthakasemsunt 2013	72/ 10180 72/10060 0/120	71/ 10187 71/10067 0/120	RR 1.01 (0.73, 1.41) 1.01 (0.73, 1.41) Not estimable	No significant difference p = 0.93 Heterogeneity NA
Pulmonary embolism TBI subgroup N = 510 (2 trials) CRASH-2 2010 Yutthakasemsunt 2013	0/253 0/133 0/120	0/257 0/137 0/120	Not estimable	Not estimable
Volume of blood transfused, mean All trauma N = 20 127 (1 trial) CRASH-2 2010	3.05 ± 7.7 (n = 10060)	3.22 ± 8.02 (n = 10067)	MD –0.17 (–0.39, 0.05)	No significant difference p = 0.13 Heterogeneity NA
Aprotinin versus placebo				
Mortality, all cause All trauma N = 70 (1 trial) McMichan 1982	0/35	3/35	0.14 (0.01, 2.67)	No significant difference p = 0.19 Heterogeneity NA
Volume of blood transfused, mean All trauma N = 70 (1 trial) McMichan 1982	1.2 ± 0.8 (n = 35)	1.6 ± 1.3 (n = 35)	MD –0.40 (–0.9, 0.11)	No significant difference p = 0.12 Heterogeneity NA
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the target population but could be sensibly applied. The study population is broader than the intended Guidelines population. CRASH-2 2010 also includes patients ***at risk*** of significant bleeding. Yutthakasemsunt, 2013 includes patient with moderate traumatic brain injury.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats CRASH-2 2010 include countries with a similar health care system as Australia but also include low and middle-income countries.				
Additional comments				
List of included studies (patients with critical bleeding) CRASH-2 2010, Yutthakasemsunt 2013, McMichan, 1982				

CI, confidence interval; ITT, intention-to-treat; MD, mean difference; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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%.

STUDY DETAILS: Cannon 2017			
Citation			
Cannon, J. W., Khan, M. A., Raja, A. S., Cohen, M. J., Como, J. J., Cotton, B. A., Dubose, J. J., Fox, E. E., Inaba, K., Rodriguez, C. J., Holcomb, J. B. & Duchesne, J. C. 2017. Damage control resuscitation in patients with severe traumatic hemorrhage: A practice management guideline from the Eastern Association for the Surgery of Trauma. *Journal of Trauma and Acute Care Surgery*, 82(3), 605-617. doi: 10.1097/TA.0000000000001333.			
Affiliation/Source of funds			
The authors declared no conflicts of interest. Author BA Cotton is a consultant, Haemonetics Corporation. Remaining authors have no affiliations to disclose. Source of funding not disclosed.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs and cohort studies (prospective and retrospective)	I / III	*Shakur 2010:* Over 40 countries *Morrison 2012:* Afghanistan *Morrison 2013:* Afghanistan *Cole 2015:* Not reported	Trauma *Shakur 2010*: Civilian *Morrison 2012:* Military *Morrison 2013:* Military *Cole 2015*: Civilian
Intervention		**Comparator**	
PICO 1: MT/DCR PICO 2: High ratio of FFP and PLT to RBCs PICO 3: rFVIIa PICO 4: TXA (dose and route of delivery not specified) Data for TXA detailed below. Data for other interventions extracted elsewhere (see Q2, Q3 and Q5).		PICO 1: No MT/DCR PICO 2: Low ratio of FFP and PLT to RBCs PICO 3: No rFVIIa PICO 4: No TXA (further details not provided)	
Population characteristics			
Patients with severe trauma at risk of death from haemorrhage, defined as patients requiring blood transfusion and/or with an injury score greater than 25 PICO 4: *Shakur 2010:* RCT in adult trauma patients; 68% with blunt mechanism of injury, 18% with Glasgow Coma Score of ≤ 8, defined by review authors as 'questionably bleeding' (p613) *Morrison 2012:* retrospective cohort study in adult trauma patients injured during military combat, 30% injured by gunshot wound, 70% injured by explosion, 29% with Glasgow Coma Score of ≤ 8 *Morrison 2013:* prospective cohort study in adult trauma patients injured during military combat *Cole 2015:* Severely injured adult trauma patients			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, Medline, Embase Search dates: Jan 1985 through December 2015 **Identified Citations were published between Jun 2010 and Feb 2015.** No information was provided on length of follow-up post TXA intervention.		Mortality (in-hospital, 28 day or 30 day) Red blood cells administered (RBC) via IV in 24, 48 or 72 hours Need for massive transfusion Venous thromboembolism; deep vein thrombosis or pulmonary embolism	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The authors did not provide a full list of excluded studies or details relating to risk of bias assessments, but GRADE profiles were presented. Information regarding individual studies were limited.			

STUDY DETAILS: Cannon 2017				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**TXA** **n/N (%)** **Mean ± SD (n)**	**No TXA** **n/N (%)** **Mean ± SD (n)**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TXA versus no TXA				
Mortality N = 21666 (1 RCT, 2 Coh) CRASH-2 2010 Cole 2015 Morrison 2013	**1550/10616 (14.6%)** 1463/10050 30/160 57/406	**1828/11050 (16.5%)** 1613/10067 36/225 179/758	**RR 0.70 (0.54, 1.20)** **RD 0.027** **OR 0.81 (0.54, 1.20)** OR 0.89 (0.83, 0.96) OR 1.21 (0.71, 2.07) OR 0.53 (0.38, 0.73)	*No significant difference* *p* = 0.29 Substantial heterogeneity I^2 = 82% (*p* < 0.04) *p* = 0.004 *p* = 0.48 *p* = 0.0001
RBC units N = 11944 (1 RCT, 2 Coh) CRASH-2 2010 Cole 2015 Morrison 2013 Cryo+ Morrison 2013 Cryo- Morrison 2013 total	**N = 5633** 6.06 ± 9.98 (5067) 7 ± 7.4 (160) 22 ± 13.2 (258) 8 ± 6.2 (148)	**N = 6311** 6.29 ± 10.31 (5160) 2 ± 5 (225) 20.1 ± 16 (168) 6 ± 0.8 (758)	**MD 2.14 (–0.36, 4.63)** –0.23 (–0.62, 0.16) 5.00 (3.68, 6.32) 1.90 (–1.01, 4.81) 2.00 (1.00, 3.00) 1.99 (1.04, 2.94)	No significant difference *p* = 0.09 Substantial heterogeneity I^2 = 96% (*p* < 0.00001) *p* = 0.25 *p* < 0.00001 *p* < 0.0001
Massive transfusion N = 1164 (1 Coh) Morrison 2013	 272/406	 111/758	 OR 11.83 (8.86, 15.79)	*Favours control* * *p* = < 0.00001 Heterogeneity NA * TXA was part of MT protocol
VTE N = 21408 (1 RCT, 2 Coh) Shakur 2010 Cole 2015 Morrison 2012	**191/10513** 168/10060 8/160 15/293	**213/10895** 201/10067 3/603 9/225	**OR 2.00 (0.53, 7.50)** **RD 0.019** 0.83 (0.68, 1.03) 1.26 (0.48, 3.35) 10.79 (3.10, 37.58)	No significant difference *p* = 0.30 Substantial heterogeneity I^2 = 88% (*p* = 0.0003)
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population but could be sensibly applied. The study populations in Morrison 2012 and Morrison 2013 have been treated for injuries caused by gunshot and explosion (30% gunshot and 70% explosion), which may not be directly relevant to the types of injuries typically encountered in Australian health care system. Details regarding the nature of injuries in Cole 2015 were not provided in this review and injury severity for Shakur 2010 was not reported, with less than 50% of participants in this study having a blood transfusion or requiring surgery. The population in CRASH-2 is therefore questionable. The majority of pooled results were derived from Shakur 2010, overall generalisability should be interpreted with caution.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. The applicability of results from Morrison 2012 and Morrison 2013 should be interpreted with caution, as both studies were conducted in a combat zone in Afghanistan. The majority of pooled results are derived from Shakur 2010, with many countries not being able to provide early access to blood products. These details are similarly not provided for Cole 2015.				
Additional comments				
Authors conclusions:				

STUDY DETAILS: Cannon 2017
TXA administration has no clear benefit in relation to reducing mortality in severely injured, bleeding adult trauma patients. Links between TXA intervention and VTE rates need to be assessed in more detail before any association can be confirmed. However, based on their qualitative analysis of the included studies, they contend that TXA intervention could have 'modest benefits' with regards to reducing mortality in the most severely injured patients with clear evidence of bleeding. They therefore conditionally recommend TXA use when managing these patients in hospital settings and suggest administration within 3 hours post injury. *List of relevant included studies:* RCTs: Shakur 2010 Prospective cohorts: Cole 2015, Morrison 2012, Morrison 2013

CI, confidence interval; Coh, cohort; ITT, intention-to-treat; MD, mean difference; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TBI, traumatic brain injury; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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%.

STUDY DETAILS: Huebner 2017			
Citation			
Huebner B.R., Dorlac, W.C., Cribari, C. 2017. Tranexamic acid use in prehospital uncontrolled haemorrhage. ***Wilderness & Environmental Medicine***, ***28,***, S50-S60. doi: 10.1016/j.wem.2016.12.006			
Affiliation/Source of funds			
No financial or material support was provided. Authorship: conception and design or to analysis and interpretation of data (BRH, WCD, CC);(2) drafting the article or revising it critically for important intellectual content (BRH,WCD); and (3) final approval of the version to be published (BRH, WCD,CC).			
Study design	**Level of evidence**	**Location**	**Setting**
Narrative review	I / IV	Various including MC study multiple countries and SC studies in UK, US, Afghanistan	Trauma
Intervention		**Comparator**	
CRASH-2; 1 g bolus of TXA followed by a 1 g infusion over 8 hrs *Morrison 2012 (MATTERs):* Not specified *Wafaisade 2016*: Not specified *Swendsen 2013*: 1 g loading dose of TXA followed by a 1 g infusion over 8 hrs *Valle 2014*: 1 g bolus followed by 1 g infusion over 8 hrs *Harvin 2015*: 1 g bolus followed by 1 g infusion of TXA over 8 hrs *Cole 2015*: 1 g administered within 3 hrs followed by 1 g infusion over 8 hrs *Eckert 2014*: Not specified		Matching placebo in all studies	
Population characteristics			
Early and prehospital use of tranexamic acid in the treatment of haemorrhaging trauma patients. *CRASH-2* – adult patients with significant traumatic haemorrhage (SBP <90 mm Hg or HR > 110 beats/min, or both) or at risk of significant haemorrhage admitted within 8 hours of injury *MATTERs* – retrospective study, patients requiring at least 1 unit of transfusion within 24 hours of combat-related injury *Wafaisade* 2016 – German Air Rescue Service trauma registry, prehospital administration in patients with potentially life-threatening injuries or evidence of critical illness, which could include respiratory and cardiac arrest *Valle 2014* – consecutive patients requiring emergency surgery and/or receiving transfusion admitted to Jackson Memorial Hospital matched to historical controls *Cole 2015* – prospective study, adult trauma patients (SB*P* < 90 mm Hg, poor response to fluids, suspected active haemorrhage) who arrived at UK urban trauma centre before and after implementation of inclusion of TXA in trauma protocol			

STUDY DETAILS: Huebner 2017	
Swendsen 2013 – retrospective study, adult trauma patients who arrived at U California Davis within 3 hours of injury with an SB*P* < 90 mm Hg, activation of MTP at ED or taken directly to operating theatre matched to historical controls *Harvin 2015* – retrospective study or adult trauma patients admitted with hyperfibrinolysis (LY30 >3% measured by TEG), before and after implementation of inclusion of TXA in trauma protocol (Houston) *Eckert 2014* – paediatric trauma patients in Afghanistan with predominantly penetrating injury (mean age 11 years)	
Length of follow-up	**Outcomes measured**
PubMed search. All published data on TXA and trauma. Additional trials currently underway relating to the use of TXA in early and prehospital settings were found on clinicaltrials.gov	All-cause mortality, hospital mortality, risk of death due to bleeding, vascular occlusive events, blood product transfusion, mean time to death, thromboembolic events, RBC required in operating room.
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The authors did not provide any specific search methods, no reference was made to excluded studies, and the risk of bias of included studies was not formally assessed.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**TXA** **n/N (%)** **Mean ± SD**	**Placebo** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
TXA vs. no TXA				
Mortality, all cause within 4 weeks of injury N = 20 211 CRASH-2	NR/NR (14.5%)	NR/NR (16.0%)	RR 0.91 (0.85, 0.97)	*Favours TXA* *p* = 0.0035
within 48 hours N = 896 MATTERs	NR/NR (NR)	NR/NR (NR)	RD 6.6% (NR)	*Favours TXA* *p* = 0.004
within 24 hours N = 5765 Wafaisade 2016 N = 1032 Harvin 2015, adjusted	NR/NR (5.8%) NR/98 (NR)	NR/NR (12.8%) NR/924 (NR)	NR OR 1.92 (1.05, 3.25)	*Favours TXA* *p* = 0.01 *Favours placebo* *p* = 0.035
timing not specified N = 126 Swendsen 2013 re-analysis (N = NR) N = 300 [b] Valle 2014 N = NR Cole 2015 (patients in shock)	NR/NR (5.8%) NR/NR (4.3%) NR/NR (27%) NR/NR (NR)	NR/NR (17.6%) NR/NR (19.1%) NR/NR (17%) NR/NR (NR)	NR NR NR OR 0.16 (0.03, 0.86)	*Favours TXA* *p* = 0.05 *p* = 0.03 *Favours placebo* *p* = 0.024 *Favours TXA*

STUDY DETAILS: Huebner 2017				
N = 766 Eckart 2014 *adjusted for confounders	NR/NR (15%)	NR/NR (9%)	OR 0.27 (0.85, 0.89)	*p* = 0.03 *Favours TXA* *p* = 0.03
In-hospital mortality N = 896 MATTERs massive transfusion subgroup (N = NR) N = 5765 Wafaisade 2016 N = 1032 Harvin 2015, adjusted	 NR/NR (NR) NR/NR (14.4%) NR/NR (14.7%) NR/98 (NR)	 NR/NR (NR) NR/NR (28.1%) NR/NR (16.3%) NR/924 (NR)	 RD 6.5% (NR) RD 13.7% (NR) RR 0.49 (NR) NR NR	 *Favours TXA* *p* = 0.03 *p* = 0.04 No significant difference NR No significant difference NR
Risk of death due to bleeding N = 20 211 (1 trial) CRASH-2	NR/NR (4.9%)	NR/NR (5.7%)	RR 0.85 (0.76, 0.96)	*Favours TXA* *NR*
Time to death, days N = 5765 (1study) Wafaisade 2016	Mean ± SD 8.8 ± 13.4	Mean ± SD 3.6 ± 4.9	MD NR	*Favours TXA* *p* = 0.001
Vascular occlusive events N = 20 211 (1 trial) CRASH-2	NR/NR (1.7%)	NR/NR (2.0%)	NR	No significant difference *NR*
Thromboembolic events N = NR (1 trials) Cole 2015	NR/NR (8%)	NR/NR (2%)	NR	*Favours placebo* *p* = 0.01
DVT/PE N = 126 (1 trial) Swendsen 2013 Swendsen 2013, re-analysis	 NR/NR (11.5%) NR/NR (12%)	 NR/NR (0%) NR/NR (0%)	 NR NR	*Favours placebo* *p* = 0.004 *p* = 0.012
Blood product transfusion N = 20 211 (1 trial) CRASH-2	NR/NR (50.4%)	NR/NR (51.3%)	NR	No significant difference *p* = 0.21
Total volume of RBC required in operating room, mL N = 300 (1 study)[b] Valle 2014	2250	1500	NR	*Favours placebo* *p* = 0.002
Total volume fluid received in ED, mL N = 300 (1 study) [b] Valle 2014	2675	2250	NR	*Favours placebo* *p* = 0.025
Total volume FFP in operating room, mL	1750	1125	NR	*Favours placebo* *p* = 0.009

STUDY DETAILS: Huebner 2017				
N = 300 (1 study) [b] Valle 2014				
CRASH-2 sub-analysis – timing of TXA administration vs. no TXA				
Mortality due to bleeding N = NR (1 trial) within 1 hour between 1 & 3 hours after 3 hours	 NR/NR (5.3%) NR/NR (4.8%) NR/NR (4.4%)	 NR/NR (7.7%) NR/NR (6.1%) NR/NR (3.1%)	 RR 0.68 (0.57, 0.82) RR 0.79 (0.64, 0.97) RR 1.44 (1.12, 1.84)	 *p* < 0.0001 *Favours TXA* *p* = 0.03 *Favours TXA* *NR Favours placebo*
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population i.e. Australian patients with uncontrolled haemorrhage due to trauma (see other comments re CRASH-2)				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats (see other comments re CRASH-2)				
Additional comments				
Authors conclusion: Our recommendation based on the current literature advocates the use of early bolus TXA in the prehospital setting in those patients at risk of significant uncontrolled bleeding. The benefit is most pronounced when given early after injury (<1 hour) and, combined with the extensive literature on prophylactic administration in elective surgery, may be most beneficial when given before the development of haemorrhagic shock. We recommend withholding repeat dosing until coagulation status has been determined and redosing at that time for a LY30 (rate of clot breakdown, lysis at 30 minutes) of 43% on TEG. *List of relevant included studies:* RCTs: CRASH-2 2010; CRASH-2 2011 (reanalysis – mortality due to bleeding, timing of administration) Cohort studies: Morrison 2012 (MATTERs); Wafaisade 2016; Valle 2014; Cole 2015; Swendsen 2013; Harvin 2015; Eckert 2014				

CI, confidence interval; DVT, deep vein thrombosis; FFP, fresh frozen plasma; ITT, intention-to-treat; NR, not reported; PE, pulmonary embolism; RCT, randomised controlled trial; RD, risk difference; RR, relative risk; SD, standard deviation; TEG, thromboelastography; TXA, Tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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%.

b. Total N not reported, calculated based on report that 150 patients who received TXA were propensity-matched to controls.

STUDY DETAILS: Nishida 2017			
Citation			
Nishida, T., Kinoshita, T. & Yamakawa, K. 2017. Tranexamic acid and trauma-induced coagulopathy. *Journal of Intensive Care,* 5(5). doi: 10.1186/s40560-016-0201-0			
Affiliation/Source of funds			
The authors stated no funding has been supplied for review. (p6) The authors declared no conflicts of interest. (p6) *Author affiliations:* Division of Trauma and Surgical Critical Care, Osaka General Medical Center, 3-1-56 Bandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs and observational studies.	I	Countries of origin for included studies not provided.	Hospital, trauma
Intervention		**Comparator**	
TXA IV; dose, frequency and duration for individual studies not specified.		Placebo, no intervention	

STUDY DETAILS: Nishida 2017				
Population characteristics				
Patients with trauma induced coagulopathy *RCTs:* *Shakur 2010*: Adult trauma patients with, or at risk of, significant bleeding *Yutthakasemsunt 2013:* Adult trauma patients with moderate to severe traumatic brain injury (post-resuscitation Glasgow Coma Scale 4 to 12) *Observational studies:* *Morrison 2012*: Patients who received at least 1 unit of PRBCs within 24 h of admission following combat-related injury *Swendsen 2013*: Adult trauma patients who met triage criteria for serious injury and at least one of the following: hypotension, massive transfusion guideline activation, or transport directly to the operating room or interventional radiology suite *Haren 2014*: Adult trauma patients with hypercoagulable state defined as Greenfield's risk assessment profile (RAP) ≥10 *Harvin 2014*: Adult trauma patients with hyperfibrinolysis determined by rapid thromboelastography *Cole 2015*: Adult trauma patients with severe injury defined as injury severity score (ISS) >15 *Wafaisade 2015*: Trauma patients with/without prehospital TXA administration				
Length of follow-up			**Outcomes measured**	
Citations published between Jun 2010 and May 2016. No information was provided on follow up post TXA intervention.			Venous thromboembolism (including deep vein thrombosis and pulmonary embolism)	
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one critical flaw with non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. The authors provide insufficient details regarding: pre-specified methods, study inclusion criteria, duplicate study selection and data extraction, risk of bias analysis, individual study characteristics, or heterogeneity analysis. No mention was made of excluded or ongoing studies, funding sources for the included studies, or potential for publication bias. Although separate summary estimates were provided for RCTs and observational studies, pooled outcomes were not adjusted for heterogeneity. *Risk of bias of included studies:* The authors did not include an appropriately detailed risk of bias analysis for the included studies. However, they do acknowledge that there is serious risk of bias due to the observational nature of six of the eight included studies, in addition to their unadjusted pooled data. The authors were also concerned by a lack of detail from some of the observational studies, regarding diagnosis, protocols or treatment for venous thromboembolisms; the primary outcome in question. They therefore contend that the overall quality of the evidence is very low.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**TXA** **n/N (%)** **Mean ± SD**	**Comparator** **n/N (%)** **Mean ± SD**	**Risk Estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TXA versus no TXA (placebo or no intervention)				
Venous thromboembolism N = 23117 (2 RCTs, 6 Coh)	**209/10881**	**288/12236**	**RR 1.32 (0.80, 2.16)**	No significant difference *p* = 0.28 Substantial heterogeneity I^2 = 61% (*p* = 0.02)
Venous thromboembolism N = 20365 (2 RCTs) Shakur 2010 Yutthakasemsunt 2013	**168/10180** 168/10060 0/120	**201/10185** 201/10067 0/118	**RR 0.84 (0.68, 1.02)** 0.84 (0.68, 1.02) Not estimable	No significant difference *p* = 0.08 Heterogeneity NA (zero events in one study)

STUDY DETAILS: Nishida 2017				
Venous thromboembolism N = 2752 (6 Coh studies)	**41/701**	**87/2051**	**RR 1.61 (0.86, 3.01)**	No significant difference *p* = 0.14 Substantial heterogeneity I^2 = 52% (*p* = 0.06)
Morrison 2012 [b]	8/293	2/603	8.23 (1.76, 38.52)	
Swendsen 2013	6/52	0/74	18.40 (1.06, 319.58)	
Haren 2014	9/27	25/94	1.25 (0.67, 2.35)	
Harvin 2014	6/98	41/934	1.39 (0.61, 3.20)	
Cole 2015	8/160	9/225	1.25 (0.49, 3.17)	
Wafaisade 2015 [b]	4/71	10/121	0.68 (0.22, 2.09)	
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population but could be sensibly applied. The individual study populations were broader than the intended Guidelines population. Shakur 2010 included patients who were *at risk* of significant bleeding, while Yutthakasemsunt 2013 included patients with traumatic brain injury. Moreover, Swendsen 2013 included a combination of serious injury and hypotension as one of their patient inclusion criteria. Insufficient information was also provided regarding the presence of critical bleeding in patient entry criteria for Haren 2014, Cole 2015 and Wafaisade 2016.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. Information on individual study countries of origin is not provided in this review. The majority of evidence is from Shakur 2010 (CRASH-2) which was conducted in over 40 countries.				
Additional comments				
Authors conclusions The authors concluded that TXA can potentially be associated with an increased risk of venous thromboembolisms. They contended that it should therefore be used with caution. However, they stated that more research is necessary in order to confirm these associations, and to determine how to both maximise survival and minimise risk of thrombotic complications for patients. *List of included studies* Shakur 2010, Morrison 2012, Yutthakasemsunt 2013, Swendsen 2013, Haren 2014, Harvin 2014, Cole 2015, Wafaisade 2015				

CI, confidence interval; MD, mean difference; NA, not applicable; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation
a. Only applicable to Level I studies with formal meta-analysis. 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%.
b. Numbers are for pulmonary embolism only.

STUDY DETAILS: El-Menyar 2018			
Citation			
El-Menyar, A., Sathian, B., Asim, M., Latifi, R. & Al-Thani, H. 2018. Efficacy of prehospital administration of tranexamic acid in trauma patients: A meta-analysis of the randomized controlled trials. *The American Journal of Emergency Medicine, 36*(6). 1079-1087. doi: 10.1016/j.ajem.2018.03.033			
Affiliation/Source of funds			
The authors declared that there were no conflicts of interest or funding for this review. (p1086) *Author affiliations:* Department of Surgery, Trauma Surgery, Clinical Research, Hamad General Hospital, Doha, Qatar; Clinical Medicine,Weill Cornell Medical School, Doha, Qatar; Department of Surgery, Westchester Medical Center, Valhalla, NY, USA; Department of Surgery, Trauma & Vascular Surgery, Hamad General Hospital, Doha, Qatar			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of observational studies.	I /III	Countries of origin for included studies not provided.	Prehospital (air rescue helicopter)
Intervention		**Comparator**	
Wafaisade 2016: TXA, prehospital, dose and delivery route not specified *Neeki 2017*: TXA, prehospital, dose and delivery route not specified		Placebo	

STUDY DETAILS: El-Menyar 2018				
Population characteristics				
Adult traumatic injury patients presenting to the emergency department requiring blood transfusion *Wafaisade 2016:* Retrospective analysis of patients who received prehospital TXA compared to a propensity-score-based matched control. No further information provided. *Neeki 2017:* adult patients with blunt or penetrating trauma resulting in signs and symptoms of haemorrhagic shock; systolic blood pressure >90 mm Hg at scene of injury, during air and/or ground medical transport, or upon arrival to designated trauma centres; any sustained blunt or penetrating injury in previous 3 hours; high risk for significant haemorrhage (estimated blood loss of 500 mL at scene accompanied with a heart rate >120; uncontrolled bleeding by direct pressure or tourniquet, major amputation of any extremity above the wrists and above the ankles)				
Length of follow-up			**Outcomes measured**	
Citations published between May 2016 and Jun 2017 Follow-up dictated by outcomes: 24 hours and 30 days post injury for mortality; length of hospital stay for morbidity.			24 hour mortality, 30 day mortality, thromboembolic events	
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. An appropriate analysis of publication bias was not conducted, and baseline population characteristics for the two studies were also insufficiently outlined. Details were also not provided regarding duplicate study selection or sources of funding for the included studies. *Risk of bias of included studies:* The overall risk of bias for the included studies was judged by the review authors to be low or unclear, with overall quality of the evidence being moderate. They suggested that any plausible bias was unlikely to significantly impact evidence quality. Notwithstanding this, the authors mention that demonstrated effects of the studies could be reduced due to confounding (plausible confounding factors not specified).				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**Prehospital TXA** **n/N (%)** **Mean ± SD**	**Placebo** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Prehospital TXA versus placebo				
24-hour mortality N = 769 (2 Coh studies) Wafaisade 2016 Neeki 2017	20/386	41/383	OR 0.49 (0.27, 0.84) 0.47 (0.25, 0.89) 0.54 (0.18, 1.66)	*Favours TXA* *NR* No significant heterogeneity I^2 = 0% (*p* = 0.82)
30-day mortality N = 769 (2 Coh studies) Wafaisade 2016 Neeki 2017	44/386	55/383	OR 0.86 (0.56, 1.32) 0.86 (0.53, 1.38) 0.87 (0.32, 2.32)	No significant difference NR No significant heterogeneity I^2 = 0% (*p* = 0.98)
Thromboembolic events N = 769 (2 Coh studies) Wafaisade 2016 Neeki 2017	6/386	12/383	OR 0.74 (0.27, 2.07) 0.67 (0.20, 2.22) 0.98 (0.14, 7.04)	No significant difference NR No significant heterogeneity I^2 = 0% (*p* = 0.75)
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. Insufficient details were provided regarding bleeding and injury status of the population in Wafaisade 2016. The patient population in Neeki 2016 appropriately represent the Guidelines target population.				

STUDY DETAILS: El-Menyar 2018
Applicability (relevance of the evidence to the Australian health care system)
The evidence is probably applicable to the Australian healthcare context with some caveats. Information on individual study countries of origin is not provided in this review. It is therefore difficult to comment on applicability.
Additional comments
Authors conclusions The authors concluded that there was evidence linking prehospital TXA administration to a significant reduction in 24 hour mortality for adult trauma patients. Their pooled analysis also indicated that prehospital TXA intervention can reduce 30 day mortality, along with the risk of thromboembolic events in this population group. However, they acknowledge that data for the latter two outcomes was not statistically significant. Furthermore, several limitations were identified for the included studies, including a lack of information on the timing and dosages of TXA administration, in addition to causes of death. The authors also point out the potential for publication bias due to a lack of grey literature. Results of the review should therefore be interpreted with caution. They therefore suggest further research via randomised controlled trials. ***List of included studies*** Wafaisade 2016, Neeki 2017

CI, confidence interval; Coh, cohort; ITT, intention-to-treat; MD, mean difference; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TBI, traumatic brain injury; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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%.

STUDY DETAILS: Gayet-Ageron 2018			
Citation			
Gayet-Ageron, A., Prieto-Merino, D., Ker, K., Shakur, H., Ageron, F., Roberts, I. 2018. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet, 391*(10116), 125-132			
Affiliation/Source of funds			
Author affiliations: Clinical Trials Unit, LSHTM, London, UK; Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland. (p3, protocol) Conflicts of interest: research grant funding from NIHR, MRC, Wellcome and the Department of Health; donations to cover cost of TXA received from pharmaceutical companies (not specified). (p3, protocol) Funding source: London School of Hygiene and Tropical Medicine, London, UK. (p3)			
Study design	**Level of evidence**	**Location**	**Setting**
Individual patient-level meta-analysis of randomised controlled trials.	I	Countries of origin not provided (both are large international multicentre trials)	Hospital; trauma
Intervention		**Comparator**	
CRASH-2: loading dose of 1 g TXA administered as soon possible, followed by a maintenance dose of 1 g TXA over eight hours *WOMAN:* 1 g TXA via IV given as soon as possible post randomisation. If bleeding continued after 30 minutes, or stopped and restarted within 24 hours after first dose, a second dose could be given.		Placebo	
Population characteristics			
Patients with acute severe bleeding *CRASH-2:* adult (> 16 years) trauma patients with, or at risk of, significant bleeding; mean age of 34.6 years (SD 14.3); mean time from injury to treatment of 2.8 hours (SD 2.1); mean systolic blood pressure of 97 mm Hg (SD 27.9). *WOMAN:* women with clinically diagnosed post-partum haemorrhage following vaginal delivery of a baby or caesarean section; mean age of 28.5 years (SD 5.7); mean time from injury to treatment of 2.8=5 hours (SD 3.4); mean systolic blood pressure of 100.8 mm Hg (SD 22.7).			

STUDY DETAILS: Gayet-Ageron 2018	
Length of follow-up	**Outcomes measured**
Citations published between Jun 2010 and Apr 2017	Primary: absence of mortality due to bleeding Secondary: mortality due to vascular occlusive event, myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis The authors conducted logistic regression model assessing: 1. overall treatment effect and homogeneity across trials 2. non-linear effect of TXA by treatment delay and interaction with trial 3. non-linear effect of TXA by treatment delay (assuming interaction in the same in both trials) All models were controlled for systolic blood pressure (5 mm Hg interval) and age (10-yr intervals), which are strong risk factors for death due to bleeding.

INTERNAL VALIDITY

Overall QUALITY of the systematic review (descriptive)

Rating (AMSTAR): High

Description: No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

The authors did not provide a list of excluded studies, nor did they assess for publication bias.

Risk of bias of included studies: The overall risk of bias for the included studies was judged by the review authors to be low. There were no concerns raised with regard to sequence generation, allocation concealment, blinding, outcome data collection or outcome data reporting for the two trials.

Notwithstanding, the authors acknowledged that certain factors within the studies *may* have impacted results, especially regarding effect of treatment delay on TXA benefit. Specifically, they suggest potential for treatment delay underestimation in trauma patients and overestimation in postpartum haemorrhage patients, respectively. The use of multiple sensitivity analyses is believed to have accounted for these factors. They also recognised the possibility for misclassification of deaths due to bleeding and vascular occlusive events. Despite this, the authors believe that the large sample sizes allow for an accurate assessment of treatment delay effects and overall outcomes.

RESULTS:

Outcome **No. patients** **(No. trials)**	**TXA** **n/N (%)** **Mean ± SD**	**placebo** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
TXA versus placebo				
Mortality, all cause N = 40138 (2 studies) CRASH-2 WOMAN	1690/20094 1463/10060 227/ 10034	1868/20044 1613/10067 255/9977	RR 0.90 (0.85, 0.96) [b] RR 0.91 (0.85, 0.97) RR 0.89 (0.74, 1.06)	*Favours intervention* *p* = 0.001 [b] No significant heterogeneity I^2 = 0% (*p* = 0.79)
Mortality, due to bleeding N = 40138 (2 studies) CRASH-2 WOMAN	644/20094 489/10060 155/10034	764/20044 574/10067 190/9977	RR 0.84 (0.76, 0.93) [b] RR 0.85 (0.76, 0.96) RR 0.81 (0.66, 1.00)	*Favours intervention* *p* = 0.001 [b] No significant heterogeneity I^2 = 0% (*p* = 0.69)
Mortality, not due to bleeding N = 40138 (2 studies) CRASH-2	1046/20094 974/10060	1104/20044 1039/10067	RR 0.95 (0.87, 1.03) [b] RR 0.94 (0.86, 1.02)	No significant difference *p* = 0.18 [b] No significant heterogeneity I^2 = 0% (*p* = 0.36)

STUDY DETAILS: Gayet-Ageron 2018				
WOMAN	72/ 10034	65/9977	RR 1.10 (0.79, 1.54)	
Mortality due to vascular occlusive event N = 40138 (2 studies) CRASH-2 WOMAN	43/20094 (0.2%) 33/10060 (0.3%) 10/10034 (0.1%)	59/20044 (0.3%) 48/10067 (0.5%) 11/9977 (0.1%)	OR 0·73 (0·49, 1·09) 0·69 (0·44, 1·08) 0·90 (0·38, 2·12)	No significant difference *p* = 0.1204 No significant heterogeneity I² = NR (*p* = 0.5956)
Myocardial infarction (fatal and non-fatal) N = 40138 (2 studies) CRASH-2 WOMAN	37/20094 (0.2%) 35/10060 (0.3%) 2/10034 (0.0%)	58/20044 (0.3%) 55/10067 (0.5%) 3/9977 (0.0%)	OR 0·64 (0·43, 0·97) 0·64 (0·42, 0·98) 0·66 (0·11, 3·95)	*Favours intervention* *p* = 0.0371 No significant heterogeneity I² = NR (*p* = 0.9788)
Stroke (fatal and non-fatal) N = 40138 (2 studies) CRASH-2 WOMAN	65/20094 (0.3%) 57/10060 (0.6%) 8/10034 (0.1%)	72/20044 (0.4%) 66/10067 6/9977 (0.1%)	OR 0·91 (0·65, 1·27) 0·87 (0·61, 1·24) 1·32 (0·46, 3·81)	No significant difference *NR* No significant heterogeneity I² = NR (*p* = 0.4647)
Pulmonary embolism (fatal and non-fatal) N = 40138 (2 studies) CRASH-2 *WOMAN*	89/20094 (0.4%) 72/10060 (0.7%) 17/10034 (0.2%)	91/20044 (0.5%) 71/10067 (0.7%) 20/9977 (0.2%)	OR 0·98 (0·73, 1·32) 1·02 (0·74, 1·42) 0·84 (0·44, 1·61)	No significant difference *NR* No significant heterogeneity I² = NR (*p* = 0.6025)
Deep vein thrombosis (fatal and non-fatal) N = 40138 (2 studies) CRASH-2 WOMAN	43/20094 (0.2%) 40/10060 (0.4%) 3/10034 (0.0%)	48/20044 (0.2%) 41/10067 (0.4%) 7/9977 (0.1%)	OR 0·90 (0·60, 1·36) 0·98 (0·63, 1·52) 0·42 (0·11, 1·64)	No significant difference *NR* No significant heterogeneity I² = NR (*p* = 0.2483)
No mortality due to bleeding [c] N = 40138 (2 studies) CRASH-2 WOMAN	18404 (96.6%) 8597 (94.6%) 9807 (98.4)	18176 (96.0%) 8454 (93.6%) 9722 (98.1%)	OR 1·20 (1·08, 1·34) 1·19 (1·05, 1·35) 1·24 (0·99, 1·53)	*Favours intervention* *p* = 0.001 No significant heterogeneity (Model 1: interaction *p* = 0.7243)
Mortality due to bleeding, by 60 minute treatment delay from injury N = 40138 (2 studies) 0-60 min 60-120 120-180 180-240	n/20040 (Excluded: 4 missing time to treatment in CRASH-2, 50 with time to treatment > 24 hours in WOMAN) 94 (1.7%) 192 (3.9%)	n/19981 (Excluded: 4 missing time to treatment in CRASH-2, 59 with time to treatment > 24 hours in WOMAN) 115 (2.2%) 283 (5.8%) 146 (5.3%)	 OR 1.26 (0.96, 1.66) OR 1.53 (1.27, 1.84) OR 1.42 (1.09, 1.83) OR 1.08 (0.76, 1.54)	No significant heterogeneity (Model 2: interaction *p* = 0.1363 with linear terms; *p* = 0.3891 with squared terms)

STUDY DETAILS: Gayet-Ageron 2018				
240-300 300-360 360-420 420-480	104 (3.8%) 61 (3.2%) 64 (4.3%) 43 (4.4%) 37 (4.0%) 20 (3.0%)	66 (3.5%) 47 (2.9%) 35 (3.6%) 30 (3.2%) 14 (2.1)	OR 0.67 (0.45, 0.98) OR 0.80 (0.51, 1.27) OR 0.78 (0.48, 1.28) OR 0.70 (0.35, 1.39)	
Effect of treatment delay on survival N = 40138 (2 studies) Administration time: Immediate 135 min 180 min	N = 20040 (Excluded: 4 missing time to treatment in CRASH-2, 50 with time to treatment > 24 hours in WOMAN)	N = 19981 (Excluded: 4 missing time to treatment in CRASH-2, 59 with time to treatment > 24 hours in WOMAN)	OR 1.72 (1.42, 2.10) OR NR (1.00, NR) OR 1.00 (NR, NR)	*Nonlinear association with increasing delay* *p* = 0.0109 *Favours immediate administration* *p* < 0.0001 *NR* *p* = not significant
Effect of treatment delay on survival Immediate (min) Immediate (max) Immediate (mean) 200 minutes	Sensitivity analysis: Random correction of up to 60 minutes treatment delay in CRASH-2 Random subtraction of up to 60 minutes treatment delay in WOMAN		OR 1.70 (1.38, 2.11) OR 1.82 (1.47, 2.25) OR 1.77 (1.43, 2.18) OR 1.00 (NR)	*Favours immediate administration* *p* = not significant
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats Patients included in the CRASH-2 study were classified as being at risk of significant bleeding, in addition to being diagnosed with major haemorrhage. Patients in the WOMAN trial were clinically diagnosed with postpartum haemorrhage, however severity of diagnosis and life-threatening nature of haemorrhage for these patients was not specified. It is therefore important to note that an unspecified percentage of the study populations are likely representative of the Guidelines target population, but overall generalisability is uncertain.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats Data from the CRASH-2 trial comes from 40 countries, with a variety of healthcare systems. The same can be said for WOMAN, where data was collected from 21 countries. It is difficult to comment on the direct applicability of the results in the context of Australian health care.				
Additional comments				
Authors' conclusions: The authors primary findings were that: - most deaths occurred on the day of onset in patient presentations covered in the included studies, with many deaths occurring within the first few hours. - TXA administration reduced mortality and myocardial infarction, but benefits decreased with treatment delay (approximately 10% decrease with every 15 minutes of delay, with no apparent treatment effect observed at 180 min delay). - TXA administration was not associated with an increase in vascular occlusive events. The authors therefore conclude that bleeding patients should receive antifibrinolytics as soon as possible, in order to maximise treatment outcomes and reduce chance of mortality in these patient populations. *List of included studies:* CRASH-2, WOMAN				

CI, confidence interval; Coh, cohort; ITT, intention-to-treat; MD, mean difference; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TBI, traumatic brain injury; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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%.

b. Calculated post-hoc using RevMan 5.3.

c. Denominator not reported. Numbers are those used in the model. Odds are "Survival from bleeding".

STUDY DETAILS: Shakur 2018			
Citation			
Shakur, H., Beaumont, D., Pavord, S., et al. 2018. Antifibrinolytic drugs for treating primary postpartum haemorrhage. *Cochrane Database of Systematic Reviews, 2018* (2) (no pagination).			
Affiliation/Source of funds			
Author affiliations: Clinical Trials Unit, London School of Hygiene & Tropical Medicine, Keppel Street, London, UK. Source of funds: No sources of support supplied Conflicts of interest: Three authors declared interests in the WOMAN trial (principal/investigator)			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic Review of RCTs	Level I	*WOMAN 2017* UK, Nigeria, Pakistan, Uganda, Kenya, Cameroon, Sudan, Tanzania, Nepal, Zambia, Albania, Democratic Republic of Congo, Bangladesh, Ethiopia, Burkina Faso, Jamaica, Ghana, Papua New Guinea, Egypt, Colombia, and Cote d'Ivoire. *Ducloy-Bouthors 2011* France	Hospital, tertiary care centres and secondary care obstetric centres.
Intervention		**Comparator**	
Standard care plus IV tranexamic acid for treatment of primary postpartum haemorrhage.		Placebo or standard care alone	
Population characteristics			
Women after birth following a pregnancy of at least 24 weeks' gestation with a diagnosis of PPH, regardless of mode of birth (vaginal or caesarean section) or other aspects of third stage management. *WOMAN 2017:* 20018 women aged 16 years or older with clinically diagnosed PPH (estimated blood loss after vaginal birth > 500 mL, or > 1000 mL after caesarean section or estimated blood loss enough to compromise the haemodynamic status of the woman). *Ducloy-Bouthors 2011:* 151 women with PPH > 800 mL within hours after vaginal birth.			
Length of follow-up		**Outcomes measured**	
Follow-up generally not specified, but usually period of hospitalisation		Mortality (due to bleeding, all cause, other than bleeding), Serious maternal morbidity (any, renal, respiratory, cardiac, or multiple organ failure), Blood loss (number with >500 mL, number with >1000 mL, mean), Shock, Coagulopathy, Transfusion (number red cell or whole blood, other products), Post-randomisation events (uterotonics used, surgical interventions to control bleeding, non-surgical interventions to control bleeding) Admission to higher level care, hysterectomy, Maternal and neonatal side effects of intervention	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. The authors planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis. (p10) *Risk of bias of included studies:* Included studies were generally at low risk of bias. Ducloy-Bouthers was at high risk of performance bias is there was no placebo, so staff would be aware of treatment allocation.			

STUDY DETAILS: Shakur 2018				
RESULTS:				
Outcome **No. patients (No. trials)**	**TXA** **n/N (%)** **Mean ± SD**	**Placebo or no TXA** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** [a] **I^2 (*p*-value)**
IV TXA versus placebo or standard care alone				
Mortality (maternal) due to bleeding N = 20172 (2 trials) WOMAN 2017, Ducloy-Bouthers 2011	155/10036 155/10036 0/77	191/9985 191/9985 0/74	0.81 (0.65, 1.00) 0.81 (0.65, 1.00) Not estimable	*Favours TXA* *p* = 0.046 *Heterogeneity* NA [b]
Mortality (maternal) due to bleeding (timing from birth) N = 20011 (1 trial) WOMAN 2017 < 1 hr 1–3 hrs > 3hrs	 49/4846 40/2674 66/2514	 60/4726 67/2682 63/2569	 0.80 (0.55, 1.16) 0.60 (0.41, 0.88) 1.07 (0.76, 1.51)	No significant difference *p* = 0.23 *Favours TXA* *p* = 0.096 No significant difference *p* = 0.70
Mortality, all causes N = 20172 (2 trials) WOMAN 2017 Ducloy-Bouthers 2011	227/10036 227/10036 0/77	256/9985 256/9985 0/74	0.88 (0.74, 1.05) 0.88 (0.74, 1.05) Not estimable	No significant difference *p* = 0.16 Heterogeneity NA [b]
Mortality (maternal) all cause (timing from birth) N = 20011 (1 trial) WOMAN 2017 < 1 hr 1–3 hrs > 3hrs	 80/4846 57/2674 90/2514	 80/4726 83/2682 92/2569	 0.98 (0.72, 1.33) 0.69 (0.49, 0.96) 1.00 (0.75, 1.33)	Authors' conclusions: *p* = 0.87 *Favours TXA* *p* = 0.028 No significant difference *p* = 1.0
Serious maternal morbidity (any) N = 20015 (1 trial) WOMAN 2017	223/10030	224/9985	0.99 (0.83, 1.19)	No significant difference *p* = 0.92 Heterogeneity NA
Serious maternal morbidity (multiple organ failure) N = 20168 (2 trials) WOMAN 2017 Ducloy-Bouthers 2011	99/10032 99/10032 0/77	105/9985 105/9985 0/74	0.94 (0.71, 1.23) 0.94 (0.71, 1.23) Not estimable	No significant difference *p* = 0.65 Heterogeneity NA [b]
Serious maternal morbidity (respiratory failure) N = 20018 (1 trial) WOMAN 2017	108/10033	124/9985	0.87 (0.67, 1.12)	No significant difference *p* = 0.27 Heterogeneity NA
Serious maternal morbidity (cardiac arrest) N = 20018 (1 trial) WOMAN 2017	110/10033	115/9985	0.95 (0.73, 1.23)	No significant difference *p* = 0.71 Heterogeneity NA

STUDY DETAILS: Shakur 2018				
Serious maternal morbidity (renal failure) N = 20169 (2 trials) WOMAN 2017 Ducloy-Bouthers 2011	129/10033 129/10033 0/77	118/9985 118/9985 0/74	1.09 (0.85, 1.39) 1.09 (0.85, 1.39) Not estimable	No significant difference *p* = 0.51 Heterogeneity NA [b]
Serious maternal morbidity (hepatic failure) N = 20169 (1 trial) WOMAN 2017	29/10033	30/9985	0.96 (0.58, 1.60)	No significant difference *p* = 0.88 Heterogeneity NA
Serious maternal morbidity (maternal seizure) N = 20169 (2 trials) WOMAN 2017 Ducloy-Bouthers 2011	33/10033 33/10033 0/77	43/9985 43/9985 0/74	0.76 (0.49, 1.20) 0.76 (0.49, 1.20) Not estimable	No significant difference *p* = 0.24 Heterogeneity NA [b]
Blood loss, 500 mL or more after randomisation N = 151 (1 trial) Ducloy-Bouthors 2011	12/77	23/74	0.50 (0.27, 0.93)	*Favours TXA* *p* = 0.029 Heterogeneity NA
Blood loss, 1000 mL or more after randomisation N = 151 (1 trial) Ducloy-Bouthors 2011	4/77	8/74	0.48 (0.15, 1.53)	No significant difference *p* = 0.21 Heterogeneity NA
Mean blood loss N = 151 (1 trial) Ducloy-Bouthors 2011	280 ± 320 (n = 77)	387 ± 409 (n = 74)	–107.00 (–224.44, 10.44)	No significant difference *p* = 0.074 Heterogeneity NA
Transfusion rate, RBC N = 20167 (2 trials) WOMAN 2017 Ducloy-Bouthers 2011	559/10110 546/10033 13/77	5446/10057 5426/9983 20/74	1.00 (0.97, 1.03) 1.00 (0.98, 1.03) 0.62 (0.34, 1.16)	No significant difference *p* = 0.074 Heterogeneity NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats Population of WOMAN 2017 and Ducloy-Bouthors, 2011 included countries with a similar health care system as Australia, however WOMAN 2017 also included low- and middle- income countries.				
Additional comments				
List of included studies (patients with critical bleeding): WOMAN 2017; Ducloy-Bouthors 2011 *List of ongoing studies that may be relevant:* Sambou 2015 (EUCTR2015-002499-26-FR) Tranexamic acid to reduce blood loss in haemorrhagic caesarean delivery: a multicenter randomised double-blind placebo controlled dose ranging study (TRACES).				

CI, confidence interval; ITT, intention-to-treat; MD, mean difference; NA, not applicable; PP, per-protocol; PPH, primary postpartum haemorrhage; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Zero events in either group in Ducloy-Bouthers 2011 (N = 151) therefore all estimable data are from one study (WOMAN 2017)

STUDY DETAILS: Chornenki 2019			
Citation			
Chornenki, NLJ., Um, KJ., Mendoza, PA., Samienezhad, A., Swarup, V., Chai-Adisaksopha, C. & Siegal, DM. 2019. Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis. *Thrombosis Research,* 179(1). 81-86. https://doi.org/10.1016/j.thromres.2019.05.003			
Affiliation/Source of funds			
Author affiliations: Three authors from the Department of Medicine at McMaster University (N.L.J.C., K.J.U., C.C.). Three authors from the Population Health Institute at McMaster University (P.A.M., A.S., V.S.). One author from both (D.M.S) Conflicts of interest: The authors declared no conflicts of interest. (p 84) *Funding:* This project was supported by a CanVECTOR research start up award to NLJC. DMS is the recipient of a Research Early Career Award from the Hamilton Health Sciences Foundation and a partnered Heart and Stroke Foundation of Canada/CanVECTOR ERLI Grant. (p 85)			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of 22 RCTs	I	Authors did not report countries of included studies	Studies relevant to PICO: **Obstetrics** Arulkumaran 2017, Gungorduk 2013, Sentilhes 2018, Sujita 2018 **Medical** Chowdhary 1986, Sprigg 2014, Sprigg 2018, Tsementzis 1990, Hillman 2002, Roos 2000 **Trauma** Shakur 2010, Fakharian 2018, Yutthakasemsunt 2013
Intervention		**Comparator**	
Arulkumaran 2017, Gungorduk 2013, Sentilhes 2018, Sujita 2018: 1g of intravenous TXA Shakur 2010: 1g intravenous TXA over 10 minutes then another 1g intravenous TXA over 8 hours. Chowdhary 1986: 1g oral or intravenous TXA every 4 hours. Fakharian 2018, Sprigg 2014, Sprigg 2018, Yutthakasemsunt, 2013: 1g intravenous TXA then 1g intravenous TXA over 8 hours. Tsementzis 1990: 9g intravenous TXA a day in six doses for 4 weeks. Hillman 2002: 1g intravenous TXA then 1g intravenous TXA 2 hours later then 1g intravenous TXA every 6 hours for up to 72 hours. Roos 2000: 1g intravenous TXA every 4 hours for one week, then 1.5g oral TXA every 6 hours for two weeks.		Arulkumaran 2017, Gungorduk 2013, Sentilhes 2018, Sujita 2018, Shakur 2010, Fakharian 2018, Sprigg 2014, Sprigg 2018, Yutthakasemsunt 2013, Tsementzis 1990, Roos 2000: Placebo comparator Chowdhary 1986, Hillman 2002: No TXA comparator	
Population characteristics			
Included studies enrolling adults with non-surgical indications for TXA (e.g. prevention or treatment of bleeding not part of a planned surgical protocol or as planned medical management) The average (mean or median) age ranged from 24 years to 69 years in the TXA group and 25 years to 68 years in the non-TXA group. *Arulkumaran 2017:* Women requiring treatment of post-partum haemorrhage. *Shakur 2010:* Patients with non-specific traumatic injury. ***Not relevant for these guidelines*** *Gungorduk 2013, Sentilhes 2018, Sujita 2018:* Women enrolled for prevention of post-partum haemorrhage. *Sprigg 2014, Sprigg 2018:* Patients with intracerebral haemorrhage. *Chowdhary 1986, Tsementzis 1990, Roos 2000, Hillman 2002:* Patients with subarachnoid haemorrhage.			

Fakharian 2018, Yutthakasemsunt 2013: Patients with traumatic brain injury.				
Length of follow-up		**Outcomes measured**		
Databases searched: MEDLINE, EMBASE and CENTRAL (from January 1985 to August 2018)		Mortality Deep vein thrombosis Pulmonary embolism Myocardial infarction Stroke		
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* A risk of bias assessment was conducted using the Cochrane Risk of Bias Tool. Five studies were judged to be at high risk of bias, 9 studies were judged to be at unclear risk of bias and 7 studies were judged low risk of bias. In a sensitivity analysis, the authors restricted analysis to studies judged to be low risk of bias and found the significant effect remained the same.				
RESULTS:				
Outcome No. patients (No. trials)	**[intervention] n/N (%) Mean ± SD**	**[comparator] n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance* *p*-value Heterogeneity[a] I^2 (*p*-value)**
TXA versus placebo/no TXA				
Mortality N = 44077 (10 studies)	2087/22014 (9.5%)	2269/22063 (10.3%)		NR
Chowdhary 1986	5/65 (7.7%)	8/64 (12.5%)	RR 0.62 (0.21, 1.78)	
Tsementzis 1990	22/50 (44.0%)	14/50 (28.0%)	RR 1.57 (0.91, 2.71)	
Roos 2000	76/229 (33.2%)	75/233 (32.2%)	RR 1.03 (0.79, 1.34)	
Hillman 2002	27/254 (10.6%)	32/251 (12.7%)	RR 0.83 (0.52, 1.35)	
Shakur 2010	1463/10060 (14.5%)	1613/10067 (16.0%)	RR 0.91 (0.85, 0.97)	
Yutthakasemsunt 2013	12/120 (10.0%)	17/118 (14.4%)	RR 0.69 (0.35, 1.39)	
Sprigg 2014	3/16 (18.8%)	2/8 (25.0%)	RR 0.75 (0.16, 3.62)	
Arulkumaran 2017	227/9985 (2.3%)	256/10033 (2.6%)	RR 0.89 (0.75, 1.06)	
Sprigg 2018	250/1161 (21.5%)	249/1164 (21.4%)	RR 1.01 (0.86, 1.18)	
Fakharian 2018	2/74 (2.7%)	3/75 (4%)	RR 0.68 (0.12, 3.93)	
Stroke N = 42808 (5 studies)	85/21424 (0.4%)	88/21384 (0.4%)	RR 1.10 (0.68, 1.78)	No significant difference *p* = 0.71
Tsementzis 1990	6/50 (12.0%)	2/50 (4.0%)	RR 3.00 (0.64, 14.16)	Mild heterogeneity I^2 = 31% (*p* = 0.21)
Shakur 2010	55/10060 (0.5%)	66/10067 (0.7%)	RR 0.83 (0.58, 1.19)	
Yutthakasemsunt 2013	0/120	3/118 (2.5%)	RR 0.14 (0.01, 2.69)	
Arulkumaran 2017	8/10033 (0.1%)	6/9985 (0.1%)	RR 1.33 (0.46, 3.82)	
Sprigg 2018	16/1161 (1.4%)	11/1164 (0.9%)	RR 1.46 (0.68, 3.13)	
Myocardial infarction N = 42470 (3 studies)	48/21254 (0.2%)	64/21216 (0.3%)	RR 0.88 (0.43, 1.84)	No significant difference *p* = 0.74
Shakur 2010	35/10060 (0.3%)	55/10067 (0.5%)	RR 0.64 (0.42, 0.97)	Moderate heterogeneity I^2 = 46% (*p* = 0.15)
Arulkumaran 2017	2/10033 (0.0%)	3/9985 (0.0%)	RR 0.66 (0.11, 3.97)	
Sprigg 2018	11/1161 (0.9%)	6/1164 (0.5%)	RR 1.84 (0.68, 4.95)	
Pulmonary embolism N = 43161 (6 studies)	113/21598 (0.5%)	116/21563 (0.5%)	OR 0.97 (0.75, 1.26)	No significant difference *p* = 0.83

Chowdhary 1986	1/65 (1.5%)	1/64 (1.6%)	OR 0.98 (0.06, 16.08)	No significant heterogeneity I^2 = 0% (p = 0.94)
Tsementzis 1990	2/50 (4.0%)	1/50 (2.0%)	OR 2.04 (0.18, 23.27)	
Roos 2000	1/229 (0.4%)	0/233	OR 3.07 (0.12, 75.65)	
Shakur 2010	72/10060 (0.7%)	71/10067 (0.7%)	OR 1.01 (0.73, 1.41)	
Arulkumaran 2017	17/10033 (0.2%)	20/9985 (0.2%)	OR 0.85 (0.44, 1.62)	
Sprigg 2018	20/1161 (1.7%)	23/1164 (2.0%)	OR 0.87 (0.47, 1.59)	
Deep Vein Thrombosis N = 46287 (6 studies)	63/23164 (0.3%)	66/23123 (0.3%)		NR
Tsementzis 1990	0/50	3/50 (6.0%)	RR 0.14 (0.01, 2.70)	
Shakur 2010	40/10060 (0.4%)	41/10067 (0.4%)	RR 0.98 (0.63, 1.51)	
Sprigg 2014	1/16 (6.25%)	0/8	RR 1.59 (0.07, 35.15)	
Arulkumaran 2017	3/10033 (0.0%)	7/9985 (0.1%)	RR 0.43 (0.11, 1.65)	
Sprigg 2018	19/1161 (1.6%)	14/1164 (1.2%)	RR 1.36 (0.69, 2.70)	
Sentilhes 2018	0/1844	1/1849 (0.1%)	RR 0.33 (0.01 (8.20)	
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population and it is hard to judge whether it is sensible to apply based on several reporting errors and limited study information				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context based on several reporting errors and limited study information				
Additional comments				
Authors conclusions: The authors have concluded that TXA significantly reduced all-cause mortality without an increased risk of venous or arterial thrombotic complications when given for prevention or treatment of non-surgical bleeding, although the optimal timing and dosing strategy are uncertain. *List of relevant included studies:* Shakur 2010, Arulkumaran 2017				

~~Strikethrough~~: study not relevant for this review

CI, confidence interval; NR, not reported; OR, odds ratio; PICO, population intervention comparator outcome; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TXA, tranexamic acid.

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Ageron 2020			
Citation			
Ageron FX, Gayet-Ageron A, Ker K, Coats TJ, Shakur-Still H and Roberts I, for the Antifibrinolytics Trials Collaboration. Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. British Journal of Anaesthesia, 2020;124 (6): 676-683			
Affiliation/Source of funds			
Author affiliations: Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London, UK; Lausanne University Hospital, Lausanne, Switzerland; University Hospitals of Geneva, Geneva, Switzerland; University of Leicester, Leicester, UK. Conflicts of interest: The authors declared no conflicts of interest. *Funding:* The study was funded by the Wellcome Trust (grant 208870 to Roberts I and Shakur-Still H).			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs (2)	I	Not reported	CRASH-2: Trauma WOMAN: Obstetrics
Intervention		**Comparator**	
CRASH-2: Tranexamic acid (dose not specified) WOMAN: Tranexamic acid (dose not specified)		CRASH-2: Placebo WOMAN: Placebo	

STUDY DETAILS: Ageron 2020				
Population characteristics				
CRASH-2: 20,211 trauma patients WOMAN: 20,060 women with postpartum haemorrhage				
Length of follow-up	**Outcomes measured**			
Databases searched: Permanent register of antifibrinolytic trials maintained by the London School of Hygiene and Tropical Medicine Clinical Trials Unit, based on MEDLINE, Embase, CENTRAL, Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform (from 1 January 1946 to 5 July 2018).	Mortality/Death Any vascular occlusive events Fatal occlusive events Myocardial infarction Stroke Pulmonary embolism Deep vein thrombosis			
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It *may* provide an accurate summary of the results of the available studies that were included in the review. The authors did not screen studies in duplicate, consider publication bias, and did not provide conflict of interest information about the included studies. *Risk of bias of included studies:* The overall risk of bias of the included studies was judged to be at low in all domains.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
Tranexamic acid versus placebo				
Mortality/Death N = 28 333 (2 studies) CRASH-2 WOMAN	434/14270 (3.0%)	597/14063 (4.3%)	RR 0.72 (0.63, 0.81)	No significant difference *p* = 0.98
	The authors stratified individual patient data by baseline risk of death as a result of bleeding and found the effectiveness of TXA did not vary by baseline risk when given within 3 h after bleeding onset (*p* = 0.51 for interaction term).			
Any vascular occlusive events N = 28 333 (2 studies) CRASH-2 WOMAN	118/14270 (0.01%)	152/14063 (0.01%)	NR	No significant difference *p* = 0.255
	The authors stratified individual patient data by baseline risk of death as a result of bleeding and found no increased risk of vascular occlusive events with tranexamic acid and it did not vary by baseline risk categories (*p* = 0.25)			
Fatal occlusive events N = 28 333 (2 studies) CRASH-2 WOMAN	27/14270 (0.00%)	40/14063 (0.00%)	NR	No significant difference *p* = 0.058
	The authors stratified individual patient data by baseline risk of death as a result of bleeding and found no increased risk of fatal vascular occlusive events with TXA and it did not vary by baseline risk categories (*p* = 0.058)			
Myocardial infarction N = 28 333 (2 studies) CRASH-2 WOMAN	24/14270 (0.00%)	46/14063 (0.00%)	NR	No significant difference *p* = 0.909
	The authors stratified individual patient data by baseline risk of death as a result of bleeding and found no increased risk of myocardial infarction with TXA and it did not vary by baseline risk categories (*p* = 0.909)			
Stroke N = 28 333 (2 studies) CRASH-2 WOMAN	32/14270 (0.00%)	42/14063 (0.00%)	NR	No significant difference *P* = 0.152
	The authors stratified individual patient data by baseline risk of death as a result of bleeding and found no increased risk of stroke with TXA and it did not vary by baseline risk categories (*p* = 0.152)			
Pulmonary embolism	54/14270 (0.00%)	56/14063 (0.00%)	NR	No significant difference

STUDY DETAILS: Ageron 2020				
N = 28 333 (2 studies) CRASH-2 WOMAN	The authors stratified individual patient data by baseline risk of death as a result of bleeding and found no increased risk of pulmonary embolism with TXA and it did not vary by baseline risk categories (p = 0.739)			p = 0.739
Deep vein thrombosis N = 28 333 (2 studies) CRASH-2 WOMAN	28/14270 (0.00%)	30/14063 (0.00%)	NR	No significant difference p = 0.214
	The authors stratified individual patient data by baseline risk of death as a result of bleeding and found no increased risk of DVT with TXA and it did not vary by baseline risk categories (p = 0.214)			
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The included studies are performed in a large cohort and are likely to be relevant to patients in Australia. Patients included in the CRASH-2 study were classified as being at risk of significant bleeding, in addition to being diagnosed with major haemorrhage. Patients in the WOMAN trial were at risk of postpartum haemorrhage, however severity of diagnosis and life-threatening nature of haemorrhage for these patients was not specified. It is therefore important to note that an unspecified percentage of the study populations are likely representative of the Guidelines target population, but overall generalisability is uncertain.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with few caveats. The systematic review did not provide the location of the included RCTs. Data from the CRASH-2 trial comes from 40 countries, with a variety of healthcare systems. The same can be said for WOMAN, where data was collected from 21 countries. It is difficult to comment on the direct applicability of the results in the context of Australian health care.				
Additional comments				
Authors conclusions: Tranexamic acid appears to be safe and effective for patients treated within 3 hours since injury. Because many deaths are in patients at low and intermediate risk, tranexamic acid use should not be restricted to the most severely injured or bleeding patients. As tranexamic acid is safe, it should be considered as an early preventive measure rather than a treatment for severe coagulopathic bleeding. *List of relevant included studies:* CRASH-2 trial, WOMAN trial				

CI, confidence interval; NR, not reported; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Della Corte 2020			
Citation			
Della Corte L, Saccone G, Locci M, Carbone L, Raffone A, Giampaolino P, Ciardulli A, Berghella V, Zullo F. Tranexamic acid for treatment of primary postpartum haemorrhage after vaginal delivery: a systematic review and meta-analysis of randomised controlled trials. The Journal of Maternal-Fetal & Neonatal Medicine, 33:5, 869-874. DOI: 10.1080/14767058.2018.1500544			
Affiliation/Source of funds			
Author affiliations: Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples "Federico II", Naples, Italy; Department of Obstetrics and Gynaecology, Catholic University of the Sacred Heart, Rome, Italy; Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynaecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, USA *Conflicts of interest:* The authors declared no conflicts of interest. *Funding:* Not reported			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs	I	Ducloy-Bouthors 2011: France WOMAN 2017: International (21 countries)	Obstetrics

STUDY DETAILS: Della Corte 2020	
Intervention	**Comparator**
Ducloy-Bouthors 2011: 4g TXA in 1 hour (loading dose) then 1g TXA per hour over 6 hours. Other interventions: 30 IU oxytocin every 30 minutes, 500 µg sulprostone in 1 hour, bladder catheter, manual removal of retained placenta. *WOMAN 2017:* 1g TXA (loading dose) plus a second dose of 1g TXA if bleeding continued after 30 min or stopped and restarted within 24 hours of the first dose. Other interventions: oxytocin, ergometrine, misoprostol, prostaglandin, uterine massage, bladder catheter, manual removal of retained placenta (if necessary), intrauterine tamponade.	Ducloy-Bouthors 2011: No treatment WOMAN 2017: Placebo
Population characteristics	
Ducloy-Bouthors 2011: Patients with PPH > 800mL *WOMAN 2017:* Patients with PPH >500mL	
Length of follow-up	**Outcomes measured**
Databases searched: Medline, EMBASE, Web of Science, SCOPUS, ClinicaTrial.gov, Ovid, and Cochrane Library (from inception to February 2018).	Maternal death due to bleeding Maternal death (all causes) Deep-vein thrombosis Pulmonary embolism Myocardial infarction Stroke Surgical intervention Blood transfusions Organ failure
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The overall risk of bias WOMAN was deemed to be low, as it was placebo controlled and double-blind. Ducloy-Bouthors was unable to be assessed for selection bias, detection bias and other bias. Ducloy-Bouthors was assessed to be at high risk of performance bias.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TXA vs no TXA/placebo				
Maternal death, all cause N = 14 335 (2 studies) Ducloy-Bouthors 2011 WOMAN 2017	148/7155 (2.1%) 0/72 148/7083 (2.1%)	172/7180 (2.4%) 0/72 172/7108 (2.4%)	RR 0.86 (0.69, 1.07)	*p* = NR
Maternal death due to bleeding N = 14 335 (2 studies) Ducloy-Bouthors 2011 WOMAN 2017	110/7155 (1.5%) 0/72 110/7083 (1.6%)	135/7180 (1.9%) 0/72 135/7108 (1.9%)	RR 0.82 (0.64, 1.05)	*p* = NR
Deep vein thrombosis N = 144 (1 study) Ducloy-Bouthors 2011	0/72	0/72	Not estimable	*p* = NR

STUDY DETAILS: Della Corte 2020				
Pulmonary embolism N = 144 (1 study) Ducloy-Bouthors 2011	0/72	0/72	Not estimable	*p* = NR
Myocardial infarction N = 144 (1 study) Ducloy-Bouthors 2011	0/72	0/72	Not estimable	*p* = NR
Stroke N = 144 (1 study) Ducloy-Bouthors 2011	0/72	0/72	Not estimable	*p* = NR
Surgical intervention N = 14 332 (2 studies) Ducloy-Bouthors 2011 WOMAN 2017	1379/7152 (19.3%) 4/72 (5.6%) 1375/7080 (19.4%)	1453/7180 (20.2%) 5/72 (6.9%) 1448/7108 (20.4%)	RR 0.95 (0.89, 1.02)	*p* = NR No significant heterogeneity I^2 = 0%
Blood transfusions N = 144 (1 study) Ducloy-Bouthors 2011	10/72 (13.9%)	13/72 (18.1%)	RR 0.77 (0.63, 1.64)	*p* = NR
Organ failure N = 144 (1 study) Ducloy-Bouthors 2011	0/72	0/72	Not estimable	*p* = NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population, and it is difficult to judge if it can be sensibly applied. The studies were performed in a large cohort of women from emerging economies.				
Applicability (relevance of the evidence to the Australian health care system)				
Ducloy-Bouthors 2011 was performed in France which has a similar healthcare system to Australia however, the WOMAN 2017 trial was conducted in 21 countries, including many low- and middle- income countries. It is therefore difficult to judge applicability to the Australian healthcare system.				
Additional comments				
Authors conclusions: In women with established primary PPH after vaginal delivery, the use of TXA reduces the risk of hysterectomy and does not increase the risk of thromboembolic events. We recommend 1g intravenous TXA soon after the diagnosis of PPH, plus a second dose of 1g TXA if bleeding continues after 30 min. *List of relevant included studies:* Ducloy-Bouthors 2011, WOMAN 2017				

CI, confidence interval; ICU, intensive care unit; IU, international units; NR, not reported; PPH, postpartum haemorrhage; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

CI, confidence interval; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Al-Jeabory 2021
Citation
Al-Jeabory M, Szarpak L, Attila K, Simpson M, Smereka A, Gasecka A, Wieszorek W, Pruc M, Koselak M, Gawel W, Checinski I, Jaguszewski M J, Filipiak K J. Efficacy and Safety of Tranexamic Acid in Emergency Trauma: A Systematic Review and Meta-Analysis. *J. Clin Med.* 2021.10.1030. https//doi.org/10.3390/jcm10051030

Affiliation/Source of funds			
Author affiliations: Outcomes Research Unit, Polish Society of Disaster Medicine, Poland; Maria Sklodowska-Curie Bialystok Oncology Center, Poland; NATO Centre of Excellence for Military Medicine, Budapest, Hungary; Central Texas Regional SWAT, Leander, USA; Department of Gastroenterology and Hepatology, Faculty of Medicine, Wroclaw Medical University, Wroclaw, Poland; Department of Cardiology, Medical University of Warsaw, Poland; Department of Cardiology, University Medical Center Utrecht, The Netherlands; Department of Emergency Medicine, Medical University of Warsaw, Poland; Maria Sklodowska-Curie Medical Academy in Warsaw, Poland; Department of Surgery, The Silesian Hospital in Opava, Czech Republic; Department of Emergency Medical Service, Wroclaw Medical University, Poland; First Department of Cardiology, Medical University of Gdansk, Poland *Conflicts of interest:* The authors declared no conflicts of interest. *Funding:* The authors declared no funding for this review.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs (3), retrospective studies (10) and prospective studies (4).	I-II/III	Adair 2020: USA Cole 2020: UK Shakur 2010 (CRASH-2): Multi-country El-Menyar 2020: Qatar Guyette 2020 (STAAMP): USA Howard 2017: USA Kakaei 2017: Iran Lipsky 2014: Israel Morrison 2012: Afghanistan Myers 2019: USA Neeki 2017: USA Neeki 2018: USA Ng 2019: Canada Rivas 2021: USA Swendsen 2012: USA Valle 2014: USA Wafaisade 2016: Germany	17 studies in the trauma setting
Intervention		**Comparator**	
All studies: TXA infusion (dose not specified)		All studies: no TXA	
Population characteristics			
Adair 2020: Combat Cole 2020: Civil Shakur 2010 (CRASH-2): Civil El-Menyar 2020: Civil Guyette 2020 (STAAMP): Civil Howard 2017: Combat Kakaei 2017: Civil Lipsky 2014: Combat Morrison 2012: Combat Myers 2019: Civil Neeki 2017: Civil Neeki 2018: Civil Ng 2019: Civil Rivas 2021: Civil Swendsen 2012: Civil Valle 2014: Civil Wafaisade 2016: Civil			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, Scopus, EMBASE, Web of Science and CENTRAL (from inception to 10 January 2021).		In-hospital mortality Any vascular occlusive event	

	Myocardial infarction Stroke Thromboembolic events Pulmonary embolism Deep vein thrombosis Coagulation failure Multiple organ failure Acute kidney failure Hepatic failure Sepsis Infection Blood product transfusion ICU length of stay Hospital length of stay

INTERNAL VALIDITY

Overall QUALITY of the systematic review (descriptive)

Rating (AMSTAR): High

Description: No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

Risk of bias of included studies: The authors determined that there were some concerns with the risk of bias in the included studies, provided in Supplemental Figure 4, 5, 6 and 7.

RESULTS:

Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TXA versus no TXA				
In-hospital mortality Civilian and combat N = 29115 (3 RCT and 11 observational)	2099/13559 (15.5%)	2547/15556 (16.4%)	OR 0.81 (0.62, 1.06)	No significant difference *p* = 0.12 Significant heterogeneity I^2 = 83% (*p* < 0.00001)
CRASH-2 2010 (RCT)	1463/10060 (14.5%)	1613/10067 (16.0%)	OR 0.89 (0.83, 0.96)	
Guyette 2020 (RCT)	37/447 (8.3%)	43/453 (9.5%)	OR 0.86 (0.54, 1.36)	
Kakaei 2017 (RCT)	3/30 (10%)	4/30 (13.3%)	OR 0.72 (0.15, 3.54)	
El-Menyar 2020	25/102 (24.5%)	30/102 (29.4%)	OR 0.78 (0.42, 1.45)	
Myers 2019	136/189 (72.0%)	161/189 (85.2%)	OR 0.45 (0.27, 0.74)	
Neeki 2017	8/128 (6.3%)	13/125 (10.4%)	OR 0.57 (0.23, 1.44)	
Neeki 2018	13/362 (3.6%)	30/362 (8.3%)	OR 0.41 (0.21, 0.80)	
Rivas 2021	106/654 (16.2%)	91/254 (35.8%)	OR 0.35 (0.25, 0.48)	
Swendsen 2013	9/52 (17.3%)	17/74 (23.0%)	OR 0.70 (0.29, 1.73)	
Valle 2014	25/109 (22.9%)	14/105 (13.3%)	OR 1.93 (0.94, 3.97)	
Wafaisade 2016	38/258 (14.7%)	42/258 (16.3%)	OR 0.89 (0.55, 1.43)	
Morrison 2012 (combat)	148/293 (50.5%)	218/603 (36.2%)	OR 1.80 (1.36, 2.39)	
Howard 2017 (combat)	82/849 (9.7%)	271/2924 (9.3%)	OR 1.05 (0.81, 1.36)	
Lipsky 2014 (combat)	6/26 (23.1%)	0/10	OR 6.66 (0.34, 129.92)	
Myocardial infarction N = 22270	45/11288 (0.4%)	64/10982 (0.6%)	OR 0.66 (0.45, 0.97)	*Favours TXA* *p* = 0.03

(5 studies)				No significant heterogeneity I^2 = 0%
Stroke N = 22270 (5 studies)	73/11288 (0.6%)	76/10982 (0.7%)	OR 0.90 (0.65, 1.24)	No significant difference *p* = 0.50 Moderate heterogeneity I^2 = 40%
Thromboembolic events N = 2271 (6 studies)	67/1308 (5.1%)	62/963 (6.4%)	OR 0.89 (0.37, 2.11)	No significant difference *p* = 0.79 Moderate heterogeneity I^2 = 60%
Pulmonary embolism N = 25 912 (5 studies)	137/12112 (1.1%)	117/13800 (0.8%)	OR 1.57 (0.79, 3.13)	No significant difference *p* = 0.20 Significant heterogeneity I^2 = 80%
Deep vein thrombosis N = 26 165 (6 studies)	105/12240 (0.9%)	105/13925 (0.8%)	OR 1.13 (0.51, 2.51)	No significant difference *p* = 0.77 Significant heterogeneity I^2 = 83%
Coagulation failure N = 385 (1 study)	5/160 (3.1%)	5/225 (2.2%)	OR 1.42 (0.40, 4.99)	No significant difference *p* = 0.58
Multiple organ failure N = 1480 (3 studies)	106/681 (15.6%)	156/799 (19.5%)	OR 0.87 (0.66, 1.16)	No significant difference *p* = 0.35 Moderate heterogeneity I^2 = 39%
Acute kidney failure N = 1011 (2 studies)	22/212 (10.4%)	17/799 (2.1%)	OR 1.97 (1.01, 3.86)	No significant difference *p* = 0.05 No significant heterogeneity I^2 = 0%
Hepatic failure N = 385 (1 study)	5/160 (3.1%)	2/225 (0.9%)	OR 1.21 (0.81, 1.82)	No significant difference *p* = 0.35
Sepsis N = 186 (1 study)	4/67 (6.0%)	8/119 (6.7%)	OR 0.88 (0.26, 3.04)	No significant difference *p* = 0.84
Infection N = 385 (1 study)	89/160 (55.6%)	113/225 (50.2%)	OR 1.24 (0.83, 1.87)	No significant difference *p* = 0.30
ICU length of stay, days N = 2693 (7 studies)	8.7 ± 11.2	7.0 ± 14.6	MD 1.35 (–0.58, 3.27)	No significant difference *p* = 0.17 Significant heterogeneity I^2 = 98%
Hospital length of stay, days N = 2693 (7 studies)	20.6 ± 24.5	17.2 ± 23.8	MD 1.18 (–3.23, 5.58)	No significant difference *p* = 0.60 Significant heterogeneity I^2 = 98%
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. 13 studies included in the systematic review were in civilian populations and is relevant to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats.				

Cole 2020 was performed in the UK and Ng 2019 was performed in Canada, both of which have similar healthcare systems to Australia.
Additional comments
Authors conclusions: The application of TXA is beneficial in severely injured patients, undergoing shock who require massive blood transfusions. Patients who undergo treatment with TXA should be monitored for clinical signs of thromboembolism, since TXA is a standalone risk factor of a thromboembolic event and the D-dimers in traumatic patients are almost always elevated. *List of relevant included studies:* Adair 2020, Cole 2020, Shakur 2010 (CRASH-2), El-Menyar 2020, Guyette 2020 (STAAMP), Howard 2017, Kakaei 2017, Lipsky 2014, Morrison 2012, Myers 2019, Neeki 2017, Neeki 2018, Ng 2019, Rivas 2021, Swendsen 2012, Valle 2014, Wafaisade 2016

CI, confidence interval; ICU, intensive care unit; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Almuwallad 2021			
Citation			
Almuwallad A, Cole E, Ross J, Perkins Z, Davenport R. The impact of prehospital TXA on mortality among bleeding trauma patients: A system review and meta-analysis. *J Trauma Acute Care Surg*. 2021;90: 901–907.			
Affiliation/Source of funds			
Author affiliations: Centre for Trauma Science, Blizzard Institute, Queen Many University, London, United Kingdom; Emergency Medical Services Department, Faculty of Applied Medical Sciences, Jazan University, Kingdom of Saudi Arabia. *Conflicts of interest:* The authors declare no conflicts of interest. *Funding:* Not reported			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs (1) and observational studies (3)	I-II/III	Guyette 2020: USA Elmenyar 2019: Qatar Neeki 2018: USA Wafasade 2016: Germany	Trauma
Intervention		**Comparator**	
Guyette 2020: TXA (dose not specified) Elmenyar 2019: TXA (dose not specified) Neeki 2018: TXA (dose not specified) Wafasade 2016: TXA (dose not specified)		Guyette 2020: no TXA Elmenyar 2019: no TXA Neeki 2018: no TXA Wafasade 2016: no TXA	
Population characteristics			
Guyette 2020: Civilian trauma patients, 18-90 years old, systolic blood pressure <90, heart rate>110. Elmenyar 2019: Civilian trauma patients,16-80 years old with ongoing significant haemorrhage, systolic blood pressure <90, heart rate >110. Neeki 2018: Civilian trauma patients, ≥18 years old with blunt or penetrating injury, signs and symptoms of haemorrhagic shock and major amputation. Wafasade 2016: Civilian trauma patients with primarily admitted trauma, critical injuries, National Advisory Committee (NACA) IV, V, and VI, admitted to trauma registry.			
Length of follow-up		**Outcomes measured**	
Databases searched: EMBASE, Medline (PubMed), BNI, EMCARE, HMIC, SCOPUS and CENTRAL. A gray literature search was performed for: World Health Organization, International Clinical Trial Registry Platform, Clinicaltrials.gov, European Clinical Trial Registry, University of Toronto Library, Google search and Google scholar (from inception-).		24-hour mortality 28-to-30-day mortality Venous thromboembolism	

STUDY DETAILS: Almuwallad 2021

INTERNAL VALIDITY

Overall QUALITY of the systematic review (descriptive)

Rating (AMSTAR): High

Description: No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

Risk of bias of included studies: The quality assessment demonstrated that the RCT was at a low risk of bias in different domains including selection bias, performance bias, detection bias, attrition bias and reporting bias. The overall risk of bias was low for the observational studies. Three studies were observational cohort studies which are known to be at risk of confounding and bias due to a lack of randomisation.

RESULTS:

Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TXA versus no TXA				
Mortality, 24 hours N = 2140 (3 studies)	38/1067 (3.6%)	62/1073 (5.8%)	OR 0.60 (0.37, 0.99)	No significant difference *p* = 0.05 Minimal heterogeneity
Wafaisade 2016	15/258 (5.8%)	32/258 (12.4%)	OR 0.44 (0.23, 0.83)	I^2 = 27% (*p* = 0.26)
Neeki 2018	7/362 (1.9%)	13/362 (3.6%)	OR 0.53 (0.21, 1.34)	
Guyette 2020	16/447 (3.6%)	17/453 (3.8%)	OR 0.95 (0.47, 1.91)	
Mortality, 28 to 30 days N = 2143 (3 studies)	85/1062 (8.0%)	117/1072 (10.9%)	OR 0.69 (0.47, 1.02)	No significant difference *p* = 0.06 Minimal heterogeneity I^2 = 38% (*p* = 0.20)
Wafaisade 2016	36/258 (14.0%)	42/258 (16.3%)	OR 0.83 (0.51, 1.35)	
Neeki 2018	13/362 (4.0%)	30/362 (8.3%)	OR 0.41 (0.21, 0.80)	
Guyette 2020	36/442 (8.1%)	45/452 (10%)	OR 0.80 (0.51, 1.27)	
Venous thromboembolism N = 2020 (4 studies)	40/982 (4.0%)	31/1038 (3.0%)	OR 1.49 (0.90, 2.46)	No significant difference *p* = 0.12 Minimal heterogeneity I^2 = 0% (*p* = 0.48)
Wafaisade 2016	4/71 (5.6%)	10/121 (8.3%)	OR 0.66 (0.20, 2.20)	
Neeki 2018	2/362 (0.6%)	2/362 0.6%)	OR 1.00 (0.14, 7.14)	
Elmenyar 2019	9/102 (8.8%)	5/102 (4.9%)	OR 1.88 (0.61, 5.81)	
Guyette 2020	25/447 (5.6%)	14/453 (3.1%)	OR 1.86 (0.95, 3.62)	

EXTERNAL VALIDITY

Generalisability (relevance of the study population to the Guidelines target population)

The evidence is directly generalisable to the Australian population.

The included studies were conducted in civilian populations. The studies were performed in a wide range of ages which is reflective of the Australian population.

Applicability (relevance of the evidence to the Australian health care system)

The evidence is probably applicable to the Australian healthcare context with some caveats.

Three studies were conducted in the USA and Qatar, which do not have similar health care systems to Australia. However, Wafaisade 2016 was conducted in Germany and therefore may be applicable to the Australian healthcare system.

Additional comments

Authors conclusions:

STUDY DETAILS: Almuwallad 2021
The review examined the impact of prehospital TXA on mortality and the incidence of VTE in bleeding trauma patients. Meta-analysis revealed a significant reduction in early (24 hours), and trend toward improving (28 to 30 days) mortality with no associated increased risk of VTE among patients who received prehospital TXA. Earlier administration of TXA either in hospital or during the prehospital phase of care is associated with greater efficacy and improved overall survival in bleeding trauma patients without an increased risk of VTE. *List of relevant included studies:* Guyette 2020, Elmenyar 2019, Neeki 2018, Wafasade 2016

CI, confidence interval; RCT, randomised controlled trial; OR, odds ratio; SD, standard deviation; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

Randomised controlled trials

STUDY DETAILS: HALT-IT 2020			
Citation			
HALT-IT Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *Lancet*. 2020 Jun 20;395(10241):1927-1936. doi: 10.1016/S0140-6736(20)30848-5.			
Affiliation/Source of funds			
Author affiliations: Author affiliations listed on pages 1934 and 1935 of the publication. Conflicts of interest: The authors declared no conflicts of interest. Funding: UK National Institute for Health Research Health Technology Assessment Programme.			
Study design	**Level of evidence**	**Location**	**Setting**
Randomised controlled trial	II	UK, Pakistan, Nigeria, Egypt, Malaysia, Georgia, Romania, Nepal, Sudan, Saudi Arabia, Spain, Ireland, Albania, Papua New Guinea, and Australia	164 hospitals
Intervention		**Comparator**	
Loading dose of 1 g tranexamic acid, which was added to 100 mL infusion bag of 0·9% sodium chloride and infused by slow intravenous injection over 10 min, followed by a maintenance dose of 3 g tranexamic acid added to 1 L of any isotonic intravenous solution and infused at 125 mg/h for 24 h		Placebo (sodium chloride 0.9%)	
Population characteristics			
Adults aged either 16 years or 18 years and older (depending on country) with significant gastrointestinal bleeding defined as a risk of bleeding to death and included patients with hypotension, tachycardia, signs of shock or those likely to need transfusion or urgent endoscopy or surgery. Mean (SD) age (yrs): 58.1 (17); suspected active bleeding: 87% to 88%; signs of shock 43% to 44%;			
Length of follow-up		**Outcomes measured**	
Participants enrolled between 4 July 2013 and 21 June 2019.		Primary outcome: - Death due to bleeding within 5 days of randomisation. Secondary outcomes: - Death due to bleeding within 24 hours and 28 days of randomisation, - All-cause and cause-specific mortality at 28 days, - rebleeding within 24 hours, within 5 days and within 28 days of randomisation, - surgery or radiological intervention, - blood product transfusion, - thromboembolic events (deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction), - seizures, - other complications (including other significant cardiac event, sepsis, pneumonia, respiratory failure, renal failure, liver failure), - days in an intensive care unit, and functional status.	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Unclear Description: The study has plausible bias that raises some doubt about the results. The primary outcome was altered during the course of the trial, with a subsequent increase in sample size. Modified intent-to-treat analysis (not including patients who did not received dose of the allocated treatment and those for whom outcome data on death were not available).			

RESULTS				
Outcome	**Intervention n/N (%) Mean ± SD**	**Comparator n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
TXA versus no TXA				
All-cause mortality N = 11 937	564/5956 (9.5)	548/5981 (9.2)	RR 1.03 (0.92, 1.16)	NR
Death due to bleeding within 24 hours N = 11 937	124/5956 (2.1)	120/5981 (2.0)	RR 1.04 (0.81, 1.33)	*NR*
Death due to bleeding within 28 days N = 11 937	253/5956 (4.2)	262/5981 (4.4)	RR 0.97 (0.82, 1.15)	NR
Rebleeding within 24 hours N = 11 937	41/5956 (0.7)	41/5981 (0.7)	RR 1.00 (0.65, 1.55)	NR
Rebleeding within 28 days N = 11 937	410/5956 (6.8)	448/5981 (7.5)	RR 0.92 (0.81, 1.05)	NR
Any thromboembolic event N = 11 929	86/5952 (14)	72/5977 (1.2)	RR 1.20 (0.88, 1.64)	NR
Venous events (deep vein thrombosis, pulmonary embolism) N =11 929	48/5952 (0.8)	26/5977 (0.4)	RR 1.85 (1.15, 2.98)	NR
Deep vein thrombosis N = 11929	23/5952 (0.4)	12/5977 (0.2)	RR 1.92 (0.96, 3.86)	NR
Pulmonary embolism N = 11 929	28/5952 (0.5)	16/5977 (0.3)	RR 1.76 (0.95, 3.24)	NR
Arterial events (myocardial infarction, stroke) N = 11 929	42/5952 (0.7)	46/5977 (0.8)	RR 0.92 (0.60, 1.39)	NR
Myocardial infarction N = 11 929	24/5952 (0.4)	28/5977 (0.5)	RR 0.86 (0.50, 1.48)	NR
Stroke N = 11 929	19/5952 (0.3)	18/5977 (0.3)	RR 1.06 (0.56, 2.02)	NR
Renal failure N = 11 929	142/5951 (2.4)	157/5978 (2.6)	RR 0.91 (0.73, 1.14)	NR
Liver failure N = 11 929	196/5952 (3.3)	184/5977 (3.1)	RR 1.07 (0.88, 1.30)	NR
Respiratory failure N = 11 930	105/5952 (1.8)	131/5978 (2.2)	RR 0.81 (0.62, 1.04)	NR
Cardiac event N = 11 929	100/5952 (1.7)	89/5977 (1.5)	RR 1.13 (0.85, 1.50)	NR
Sepsis N = 11 929	210/5952 (3.5)	216/5977 (3.6)	RR 0.98 (0.81, 1.18)	NR
Pneumonia	193/5952 (3.2)	174/5978 (2.9)	RR 1.11 (0.91, 1.36)	NR

N = 11 930				
Seizure N = 11 929	38/5952 (0.6)	22/5977 (0.4)	RR 1.73 (1.03, 2.93)	NR
Whole blood or RBC transfused, units N = NR	2·8 ± 2·4	2·9 ± 2·7	MD –0.06 (0.05, –0.18)	NR
FFP transfused, units N = NR	0·9 ± 2·4	1·0 ± 2·6	MD –0·05 (–0·01, –0·23)	NR
Platelets transfused, units N = NR	0·2 ± 0·9	0·2 ± 1·0	MD –0·02 (0·02, –0·06)	NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The study included patients treated in Australia, however also included various other countries such as Saudi Arabia, Sudan and Pakistan).				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context.				
Additional comments				
Authors conclusions: Tranexamic acid did not reduce death from gastrointestinal bleeding but was associated with an increased risk of venous thromboembolic events and seizures.				

CI, confidence interval; h, hours; NR, not reported; RBC, red blood cells; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; TXA, tranexamic acid; UK, United Kingdom

Observational / cohort studies

STUDY DETAILS: Myers 2019			
Citation			
Myers, SP., Kutcher, ME., Rosengart, MR., Sperry, JL., Peitzman, AB., Brown, JB. & Neal,MD. 2019. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *Journal of Trauma and Acute Care Surgery, 86*(1). 20-27. doi: 10.1097/TA.0000000000002061			
Affiliation/Source of funds			
Author affiliations: Department of General Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Division of Trauma and Critical Care, University of Mississippi Medical Center, Jackson, Mississippi. *Conflict of interest:* M.D.N. is an external scientific advisor to Janssen Pharmaceuticals. Remaining authors have no conflicts dedclared. *Funding:* The authors declared no sources of funding			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort	III-3	USA (Pittsburgh)	Level 1 Trauma Centre
Intervention		**Comparator**	
Treated with TXA within three hours of presentation The authors do not mention the manner of administering TXA or how much the dosage was.		No TXA administered to patient	
Population characteristics			
Median age: 36 (TXA), 32 (unexposed) Female: 104/378 (27.5%) Mean weight: 85.95kg			
Length of follow-up		**Outcomes measured**	
21931 people were eligible for the study from 2012-2016. 2651 patients were excluded based on: - Prehospital anticoagulation = 2499 - Received pre-hospital TXA = 10 - Known history of DVT/PE/ hereditary coagulopathy = 142		VTE (primary outcome) including DVT and PE Survival, transfusion, ICU and hospital lengths of stay (secondary outcomes).	
Method of analysis			
Propensity Score Matching: used to match each exposed person with an unexposed person with similar personal characteristics. Aims to equally distribute confounders amongst both groups and simulate random selection of people to exposed group.			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study has some important problems and cannot be considered comparable to a well-performed randomised trial.			
RESULTS			

Population analysed	**Intervention**		**Comparator**	
Available	217		19 280	
Analysed	189		189	
Outcome	**Intervention n/N (%) Mean ± SD**	**Comparator n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
TXA versus no TXA				
VTE N = 378	29/189 (15.3%)	14/189 (7.4%)	Adjusted OR 3.26 (1.3, 9.1)	*Favours intervention* *p* = 0.02
Survival N = 378	136/189 (72%)	161/189 (85%)	Adjusted OR 0.86 (0.23, 3.25)	No significant difference *p* = 0.83

STUDY DETAILS: Myers 2019				
Patients requiring transfusion N = 378	156/189 (89%)	119/189 (64%)	NR	*Favours intervention* *p* < 0.001
Length of stay in ICU, mean N = 378	189/378 9.4 days ± 9.05	189/378 6.5 days ± 7.2	NR	*Favours intervention* *p* < 0.001
Length of stay in hospital, mean N = 378	189/378 18.2 days ± 17.3	189/378 10.9 days ± 10.9	NR	*Favours intervention* *p* < 0.001
Transfusion of platelets, units N = 378	1.18 ± 2.17	0.43 ± 1.43	NR	*Favours intervention* *p* < 0.001
Transfusion of packed RBCs, units N = 378	4.43 ± 5.57	2.53 ± 3.35	NR	*Favours intervention* *p* < 0.001
Transfusion of FFP, units N = 378	2.77 ± 5.14	1.44 ± 3.37	NR	*Favours intervention* *p* < 0.001
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats.				
Additional comments				
Authors conclusions: Our data demonstrates that TXA may be an independent risk factor for VTE development, but was not associated with a survival benefit in this single-center cohort study				

aOR, adjusted odds ratio; CI, confidence interval; DVT, deep vein thrombosis; FFP, fresh frozen plasma; ICU, intensive care unit; NR, not reported; PE, pulmonary embolus; RBC, red blood cell; SD, standard deviation; TXA, tranexamic acid; VTE, venous thromboembolism.

E8 Viscoelastic testing (Question 8)

Systematic reviews/meta-analyses

STUDY DETAILS: Da Luz 2014			
Citation			
Da Luz, L. T., Nascimento, B., Shankarakutty, A. K., Rizoli, S., & Adhikari, N. K. J. (2014). Effect of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: Descriptive systematic review. Critical Care, 18 (5) (no pagination)(518). doi:http://dx.doi.org/10.1186/s13054-014-0518-9			
Affiliation/Source of funds			
The study was funded by a National Blood Foundation Grant. *Author affiliations:* Dr. Rizoli is a member of a Scientific Advisory Board to CSL Behring, manufacturer of fibrinogen concentrate. He is also the recipient of a Canadian Institute of Health Research (CIHR) New Investigator award in partnership with NovoNordisk Canada, manufacturer of NovoSeven (recombinant factor VII).			
Study design	**Level of evidence**	**Location**	**Setting**
Descriptive systematic review of RCTs and observational studies (0 RCTs identified)	I /III	Countries of included studies not provided	SC, Trauma
Intervention		**Comparator**	
TEG/ROTEM guided transfusion *TEG:* Kashuk 2012, Tapia 2013 *ROTEM:* Schöchl 2010, Schöchl 2011		Standard of care	
Population characteristics			
Only studies reporting effect of TEG/ROTEM guided transfusion reported here. Kashuk 2012: Coh study in adult trauma patients transfused with at least 6 U RBCs in the first 6 hours (62% ISS ≥ 36) before/after implementation of TEG-guidance Schöchl 2010: Retrospective Coh study in massively bleeding adult trauma patients Schöchl 2011: Coh study in massively bleeding adult trauma patients (with historical controls at different centre) Tapia 2013: before/after Coh study in adult trauma patients (blunt and penetrating) transfused with at least 6 U RBCs in the first 24 hrs guided by TEG (pre-MTP) vs MTP protocol			
Length of follow-up		**Outcomes measured**	
Medline, Embase, Cochrane Controlled trials register Citations published between database inception/1946 to Feb 2014		Diagnosis of coagulopathies Transfusion management (prediction of massive transfusion and transfusion guidance) Mortality (prediction and reduction)	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review. No quantitative meta-analysis was performed. *Risk of bias of included studies:* Authors used the Newcastle-Ottawa Quality Assessment scale for cohort studies (more stars denote higher quality, range 1–9). Scores are noted below. The overall quality of included studies was judged by the review authors to be moderate. Main concerns with the use of appropriate controls. Schöchl 2010 and Schöchl 2011 – both scored 6 out of 9 Kashuk 2012 and Tapia 2013 – both scored 8 out of 9			

STUDY DETAILS: Da Luz 2014				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**TEG/ROTEM** **n/N (%)** **Mean ± SD**	**Standard of care** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TEG/ROTEM-guided transfusion versus No TEG/ROTEM				
Mortality N = 68 (1 Coh) Kashuk 2012 [b]	10/34 (29%)	20/34 (58%)	NR	*Favours TEG (p = 0.02)* *not adjusted for confounders
N = 131 (1 Coh) Schöchl 2010 (FP, PLT, PCC- guided) (subgroup: excluding TBI)	NR (24.4%) NR (14%)	NR (33.7%) TRISS predicted NR (28.7%) RISC predicted NR (27.8%) TRISS predicted NR (24.3%) RISC predicted	NR NR NR NR	*p* = 0.032 *p* > 0.05 NR NR
N = 681 Schöchl 2011 [b] (FC & PCC vs FFP)	6/80 (7.5%)	60/601 (10%)	NR	No association *p* = 0.69
N = 289 Tapia 2013 [b] (patients receiving > 6U RBC) (subgroup: patients with penetrating trauma receiving > 10 U RBCs)	41/165 (25) NR	35/124 (28) NR	NR NR	No association observed in multivariate analysis [c] *Favours TEG* NR
RBC transfusion avoided N = 681 (1 Coh) Schöchl 2011 (FC & PCC-guided vs FFP-guided)	NR/80 (29%)	NR/601 (3%)	NR	*p* < 0.001
N = 68 (1 Coh) Kashuk 2012 subgroup (patients with MRTG > 9.2)	NR	NR	NR	*Favours TEG* *p* = 0.048 *not adjusted for confounders
PLT transfusion avoided N = 681 (1 Coh) Schöchl 2011 (FC&PCC-guided vs FF*P*-guided)	NR/80 (91%)	NR/601 (56%)	NR	*p* < 0.001
N = 68 (1 Coh) Kashuk 2012 subgroup (patients with MRTG > 9.2)	NR	NR	NR	*Favours TEG* *p* = 0.03 *not adjusted for confounders
CRYO transfusion avoided N = 68 (1 Coh) Kashuk 2012 subgroup (patients with MRTG > 9.2)				*Favours TEG* *p* = 0.04 *not adjusted for confounders
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				

STUDY DETAILS: Da Luz 2014
Applicability (relevance of the evidence to the Australian health care system)
The evidence is probably applicable to the Australian healthcare context with some caveats
Additional comments
Authors conclusions: There is limited evidence from observational data that TEG/ROTEM diagnose early trauma coagulopathy and may predict blood transfusion and mortality. Effects remain unproven in RCTs. *List of included studies* 55 studies met their inclusion criteria (0 RCTs; 38 prospective Coh; 15 retrospective Coh; 2 before-after) Only studies reporting effect of TEG/ROTEM guided transfusion reported here.

CI, confidence interval; ISS, injury severity score; ITT, intention-to-treat; MD, mean difference; MRTG, maximum rate of thrombin formation; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SC, single centre; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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%.

b. Data retrieved from primary study

c. Tapia 2013 noted RBC transfusion volume as in independent predictor of mortality.

STUDY DETAILS: Haas 2014			
Citation			
Haas, T., Görlinger, K., Grassetto, A., Agostini, V., Simioni, P., Nardi, G., & Ranucci, M. (2014). Thromboelastometry for guiding bleeding management of the critically ill patient: a systematic review of the literature. *Minerva Anestesiologica*, 80(12), 1320-1335.			
Affiliation/Source of funds			
The authors declared that the study received no funding. The authors declared the following conflicts: CSL Behring, Octapharma, TEM International, Fresenius Kabi, Ve rum, Diagnostica, Sangart, Roche Diagnostics, Grifols SA, Novo Nordisk and Medtronic. Klaus Görlinger is the Medical Director of TEM International.			
Study design	**Level of evidence**	**Location**	**Setting**
Narrative review	I /III	*Trauma* Schöchl 2010, 2011: Germany Görlinger 2012a, Nienaber 2011: Austria/Germany Schaden 2012: Austria *Cardiac and aortic surgery* NR *Liver transplant* Noval-Padillo 2010: Spain Trzebicki 2010, Görlinger 2012b: NR	Trauma, SC and registries Cardiac and aortic surgery, SC Liver transplant
Intervention		**Comparator**	
ROTEM-guided transfusion algorithm **Trauma** Schöchl 2010: guidance of FC, PCC, PLT Schöchl 2011: FC, PCC Nienaber 2011: FC, PCC Görlinger 2012a: NR Schaden 2012: NR **Cardiac and aortic surgery** Rahe-Meyer 2013: FC- guidance Weber 2012: NR (with Multiplate) Girdauskas 2010: (with Multiplate), use of protamine, TXA, FFP, FC, PLT, PCC		*Standard of care* **Trauma** Schöchl 2010: TRISS prediction Schöchl 2011: FFP Nienaber 2011: FFP:RBC 1:1 Görlinger 2012a: NR Schaden 2012: Clinician discretion **Cardiac and aortic surgery** Rahe-Meyer 2013: SoC with FFP and PLTs Weber 2012: Conventional tests Girdauskas 2010: Clinical judgement, use of protamine, TXA, FFP, FC, PLT, PCC	

STUDY DETAILS: Haas 2014	
Fassl 2013: NR Hanke 2012: NR Hvas 2012: NR Görlinger 2011: NR Romlin 2011: NR Rahe-Meyer 2009a: FFP- or FC- guidance to targeted FIBTEM MCF of 22 mm Rahe-Meyer 2009b: FC- guidance to targeted FIBTEM MCF of 22 mm Anderson 2006: RBC, FFP, PLT	Fassl 2013: NR Hanke 2012: NR Hvas 2012: Clinical judgement Görlinger 2011: NR Romlin 2011: NR Rahe-Meyer 2009a: SoC Rahe-Meyer 2009b: SoC Anderson 2006: RBC, FFP, PLT
Liver transplant Noval-Padillo 2010: allogenic blood products Trzebicki 2010: blood products including TXA Görlinger 2012b: blood products	**Liver transplant** Noval-Padillo 2010: allogenic blood products Trzebicki 2010: blood products NOT including TXA Görlinger 2012b: blood products
Population characteristics	
Trauma Schaden 2012: RCT, 30 patients undergoing surgical excision of burn wounds Schöchl 2010: Retrospective analysis of 131 severe trauma patients who receive >5 U PRBCs within 24hrs of arrival at emergency. Schöchl 2011: 601 patients from German trauma registry matched with 80 controls from Austria Trauma centre. [a] Nienaber 2011: 18 patients from German trauma registry matched with 18 controls from Innsbruck trauma database. [b] Görlinger 2012a: Retrospective analysis of 5590 trauma patients before and after implementation of ROTEM-guided transfusion protocol ***Cardiac and aortic surgery*** Rahe-Meyer 2013: RCT in 61 patients undergoing aortic replacement surgery Weber 2012: RCT in 100 patients undergoing complex cardiac surgery with diffuse bleeding after heparin reversal with protamine Girdauskas 2010: RCT in 56 patients undergoing aortic surgery with hypothermic circulatory arrest Fassl 2013: SC, retrospective cohort study in 194 patients undergoing elective and urgent cardiac surgery with hypothermic circulatory arrest Hanke 2012: Cohort study with matched historical controls in 10 patients undergoing aortic arch replacement Hvas 2012: Cohort study with historical control in 1676 cardiac surgery patients Görlinger 2011: Retrospective before and after cohort study in 3865 patients undergoing cardiac surgery Romlin 2011: Cohort study with matched historical controls in 100 paediatric patients undergoing cardiac surgery Rahe-Meyer 2009a: Cohort study (pilot) with historical controls in 57 patients undergoing elective aortic valve replacement Rahe-Meyer 2009b: Cohort study (pilot) with historical controls in 18 patients undergoing thoracoabdominal aortic aneurysm Anderson 2006: SC, retrospective before and after cohort in 990 patients undergoing cardiac surgery ***Liver transplant*** Noval-Padillo 2010: Prospective before and after cohort study (pilot) in 79 patients undergoing liver transplant Trzebicki 2010: Retrospective before and after cohort study in 78 patients undergoing liver transplant. Görlinger 2012b: Retrospective before and after cohort study in 5338 patients undergoing visceral surgery or liver transplant. **Postpartum haemorrhage** No comparative studies	
Length of follow-up	**Outcomes measured**
Literature search details not provided	Outcomes reported in studies
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Critically low	

STUDY DETAILS: Haas 2014				
Description: More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. No description of literature search or study selection provided. The authors did not describe any formal quality assessment of included studies. *Risk of bias of included studies:* The quality of the evidence was judged to be moderate, i.e. that further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate. The authors did not describe any formal quality assessment of included studies.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**ROTEM** **n/N (%)** **Mean ± SD**	**Standard of care** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** [a] **I^2 (*p*-value)**
Trauma setting				
Mortality		(TRISS-predicted)		*Favours ROTEM*
N = 131 Schöchl 2010 (excluding 17 patients with TBI)	NR (24.4%) NR (14%)	NR (33.7%) NR (27.8%)	NR NR	*p* = 0.032 *p* = 0.0018
N = 681 Schöchl 2011 [a]	NR/601 (NR)	NR/80 (NR)	NR	No difference, NR
N = 36 Nienaber 2011 [b]	5/18 (13.9)	2/18 (11.1)	NR	No difference, *p* = 0.500
Allogenic blood products transfused	Cumulative (range)	Cumulative (range)		*Favours ROTEM*
N = 30				
Schaden 2012	3.0 (1.3—5.5)	9.0 (6.0—12.3)	NR	*p* = 0.002
RBC transfusion volume, units	Median (IQR)	Median (IQR)		*Favours ROTEM*
N = 36				
Nienaber 2011[b]				
>0–6 h after admission	1 (0—3)	7.5 (4—12)	NR	*p* < 0.005
>24 h after admission	3 (0—5)	12.5 (8—20)	NR	*p* < 0.005
RBC transfusion volume, units	Units per year	Units per year		*Favours ROTEM*
N = 5590				
Görlinger 2012a [d]	888	1332	33% reduction	NR
FFP transfusion volume, units	Cumulative (range)	Cumulative (range)		*Favours ROTEM*
N = 30				
Schaden 2012	0	5.0 (1.5—7.5)	NR	*p* < 0.001
FFP transfusion volume, units	Units per year	Units per year		*Favours ROTEM*
N = 5590				
Görlinger 2012a [d]	261	1221	79% reduction	NR
PLT transfusion volume, units	Units per year	Units per year		*Favours ROTEM*
N = 5590				
Görlinger 2012a [d]	29	82	65% reduction	NR
RBC transfusion need				*Favours ROTEM*
N = 681				
Schöchl 2011 [a]	NR (71%)	NR (97%)	NR	*p* < 0.001
PLT transfusion avoided				*Favours ROTEM*
N = 681				
Schöchl 2011 [a]	NR (56%)	NR (91%)	NR	*p* < 0.001
Multiple organ failure				*Favours ROTEM*

STUDY DETAILS: Haas 2014				
N = 36 Nienaber 2011[b]	3/18 (16.7)	11/18 (61.1)	NR	*p* = 0.015
Cardiac and aortic surgery				
Mortality, 6 month N = 100 Weber 2012	NR/NR (4)	NR/NR (20)	NR	*Favours ROTEM* *p* = 0.013
24 h transfusion volume, units N = 61 Rahe-Meyer 2013 N = 56 Girdauskas 2010	Median (IQR) 2 (NR) 9 (2—30)	Median (IQR) 12 (NR) 16 (9—23)	 NR NR	*Favours ROTEM* *p* < 0.001 NR
RBC transfusion volume, units N = 1676 Hvas 2012 N = 57 Rahe-Meyer 2009a FFP vs control FC vs control N = 18 Rahe-Meyer 2009b	Mean ± SD (n) 4.1 ± NR (NR) 8.2 ± NR (5) 0.7 ± NR (10) 2.5 ± NR (6)	Mean ± SD (n) 5.1 ± NR (NR) 8.5 ± NR (42) 8.5 ± NR (42) 16.4 ± NR (12)	MD 1.0 ± NR NR NR NR	*Favours ROTEM* *p* = 0.04 NR NR NR
RBC transfusion volume, units N = 100 Weber 2012	Median (IQR) 3 (2—6)	Median (IQR) 5 (4—9)		*Favours ROTEM* *p* < 0.001
FFP transfusion volume, units N = 10 Hanke 2012	Mean ± SD (n) 1.6 ± 2.2 (5)	Mean ± SD (n) 9.2 ± 6.6 (5)	NR	*Favours ROTEM* *p* = 0.038
FFP transfusion volume, units N = 100 Weber 2012	Median (IQR) 0 (0—3)	Median (IQR) 5 (3—8)	NR	*Favours ROTEM* *p* < 0.001
PLT transfusion volume, units N = 100 Weber 2012	Median (IQR) 2 (0—2)	Median (IQR) 2 (0—5)	NR	*Favours ROTEM* *p* = 0.01
Need for massive transfusion (≥ 10 U RBCs) N = 10 Hanke 2012 N = 56 Girdauskas 2010 N = 3865 Görlinger 2011	 NR NR NR/2147 (1.26)	 NR NR NR/1718 (2.5)	 NR OR 0.45 (0.2, 0.9) NR	*Favours ROTEM* NR *p* = 0.03 *p* = 0.0057
Allogenic transfusion N = 100 Romlin 2011 N = 3865 Görlinger 2011	 32/50 (64) NR/2147 (42.2)	 46/50 (92) NR/1718 (52.5)	 NR NR	*Favours ROTEM* *p* < 0.001 *p* < 0.0001
RBC transfusion N = 990 Anderson 2006 N = 194 Fassl 2013 N = 1676 Hvas 2012 N = 61 Rahe-Meyer 2013 N = 3865 Görlinger 2011	 NR (53) NR/153 (41) NR/865 (36.3) NR/NR (55) NR/2147 (40.4)	 NR (60) NR/41 (78) NR/811 (38.6) NR/NR (100) NR/1718 (49.7)	 NR NR NR NR NR	 NR *Favours ROTEM, p < 0.001* No difference, *p = 0.49* NR *p < 0.0001*

STUDY DETAILS: Haas 2014				
FFP transfusion N = 990 Anderson 2006 N = 194 Fassl 2013 N = 3865 Görlinger 2011	 NR (12) NR/153 (22) NR/2147 (1.1)	 NR (17) NR/41 (71) NR/1718 (19.4)	 NR NR NR	NR *p < 0.001* *p < 0.0001*
PLT transfusion N = 990 Anderson 2006 N = 194 Fassl 2013 N = 3865 Görlinger 2011	 NR (11) NR/153 (11) NR/2147 (10.1)	 NR (16) NR/41 (16) NR/1718 (13)	 NR NR NR	 NR *p = 0.028* *p = 0.0041*
FC transfusion need N = 1676 Hvas 2012	 NR/865 (11.6)	 NR/811 (3.6)	 NR	*Favours SoC* *p* < 0.001
Composite TEs N = 3865 Görlinger 2011	 NR/2147 (1.77)	 NR/1718 (3.19)	 NR	*Favours ROTEM* *p* = 0.011
Composite AEs (ARF, sepsis, TE, reaction) N = 100 Weber 2012	 NR/NR (8)	 NR/NR (38)	 NR	*Favours ROTEM* *p* < 0.001
Postoperative mechanical ventilation time, min N = 100 Weber 2012	Median (IQR) 316 (230—513)	Median (IQR) 827 (440—2835)	 NR	*Favours ROTEM* *p* < 0.001
Length of ICU stay, hrs N = 100 Weber 2012	Median (IQR) 21 (18—31)	Median (IQR) 24 (20—87)	 NR	*Favours ROTEM* *p* = 0.019
Liver transplant				
RBC transfusion volume, units N = 78 Trzebicki 2010 [e]	Mean ± SD (n) 4.1 ± 4.76 (39)	Mean ± SD (n) 5.53 ± 4.89 (39)	MD NR	No significant difference *p = 0.217*
RBC transfusion volume, units N = 79 Noval-Padillo 2010	Units per patient 3.9	units per patient 8.4	 53% reduction	*Favours ROTEM* NR
RBC transfusion volume, units N = 5338 Görlinger 2012b	Units per year 1319	Units per year 3454	 62% reduction	*Favours ROTEM* NR
FFP transfusion volume, units N = 78 Trzebicki 2010 [e]	Mean ± SD (n) 10.07 ± 7.47 (39)	Mean ± SD (n) 13.15 ± 6.62 (39)	MD NR	*Favours ROTEM* *p = 0.06*
FFP transfusion volume, units N = 79 Noval-Padillo 2010	Units per patient 1.9	Units per patient 5.6	 65% reduction	*Favours ROTEM* NR
FFP transfusion volume, units	Units per year	Units per year		*Favours ROTEM*

STUDY DETAILS: Haas 2014				
N = 5338 Görlinger 2012b [d]	223	4465	95% reduction	*NR*
PLT transfusion volume, mL N = 78 Trzebicki 2010 [d,e]	Mean ± SD (n) 168 ± NR (39)	Mean ± SD (n) 89 ± NR (39)	 NR	*Favours SoC* *p = 0.09*
PLT transfusion volume, units N = 79 Noval-Padillo 2010	Units per patient 0.7	Units per patient 1.5	 50% reduction	*Favours ROTEM* NR
PLT transfusion volume, units N = 5338 Görlinger 2012b [d]	Units per year 149	Units per year 433	 66% reduction	*Favours ROTEM* NR
FC required, g N = 5338 Görlinger 2012b [d]	g per year 745	g per year 68	 9.9-fold increase	*Favours SoC* NR
PCC required, IU N = 5338 Görlinger 2012b [d]	IU per year 238 500	IU per year 65 500	 2.6-fold increase	*Favours SoC* NR
Transfusion avoided N = 79 Noval-Padillo 2010	 4/20 (20)	 2/59 (3.5)	 NR	 NR
Need for massive transfusion (≥ 10 U RBCs) N = 5338 Görlinger 2012b [d]	 NR (0.88)	 NR (2.56)	 NR	*Favours ROTEM* *p* < 0.0001
RBC transfusion need N = 79 Noval-Padillo 2010[d]	 13/20 (65)	 57/59 (97)	 NR	 NR
FFP transfusion need N =79 Noval-Padillo 2010 [d]	 8/20 (40)	 47/59 (80)	 NR	 NR
PLT transfusion need N = 157 (2 RCTs) N = 79 Noval-Padillo 2010 [d] N = 78 Trzebicki 2010 [d,e]	 10/20 (50) 16/39 (41)	 40/59 (68) 11/39 (28)	 NR NR	 NR *p* = 0.23
FC transfusion need N = 79 Noval-Padillo 2010 [d]	 9/20 (45)	 59/59 (100)	 NR	 NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: Traumatic coagulopathy is typically combined with the need to restore fibrinogen levels. This need can be ideally detected and guided by ROTEM® analysis.				

STUDY DETAILS: Haas 2014			
Clinical setting	**Strength of recommendation**	**Quality of evidence**	**Comments**
Severe trauma	Strong	Moderate	Only one RCT demonstrated reduction in allogeneic blood transfusion using a ROTEM®-based algorithm. Further research to define safe and reliable thresholds for the ROTEM® to initiate coagulation therapy is urgently needed
Cardiovascular surgery	Strong	High	Three RCTs demonstrated efficacy in reducing blood loss and transfusion needs, however further research is warranted
Liver transplant	Strong	Low	Observational studies consistently demonstrate a reduction on blood product use
Postpartum haemorrhage	Weak	Low	Observational studies show the important of fast assessment for changes in haemostasis but studies providing safe thresholds are urgently needed

List of included studies:

Trauma: Schöchl 2010, Schöchl 2011, Görlinger 2012a, Nienaber 2011, Schaden 2012

Cardiac: Anderson 2006, Fassl 2013, Hvas 2012, Rahe-Meyer 2009a, Rahe-Meyer 2009b, Hanke 2012, Rahe-Meyer 2013, Girdauskas 2010, Romlin 2011, Görlinger 2011, Weber 2012

Liver transplant: Noval-Padillo 2010, Trzebicki 2010, Görlinger 2012b

ARF, acute renal failure; CI, confidence interval; FC, fibrinogen concentrate; FFP, fresh frozen plasma; g, gram; RCT, randomised controlled trial; IQR, interquartile rage; IU, international units; NR, not reported; PCC, prothrombin complex concentrate; RBC, red blood cell; ROTEM, rotational thromboelastometry; SD, standard deviation; SoC, standard of care; TEG, thromboelastography; TXA, tranexamic acid

a. Schöchl 2011 compared ROTEM-guided administration of FC and PCC with standard care guided transfusion in patients receiving >2 units FFP (no FC or PCC). Patients in intervention group received median 6 g FC (range 0—15) and 1200 IU PCC (range 0—6600) and those in the comparator group received median 6 Units FFP (range 2—51).

b. Neinaber 2011 compared ROTEM-guided administration of FC and PCC with standard care guided transfusion of 1:1 FFP:RBC ratio.

c. Multivariate regression analysis

d. Data from primary study.

e. Three patients in the intervention group (7.7%) had severe fibrinolysis and were treated with TXA.

STUDY DETAILS: Corredor 2015			
Citation			
Corredor, C., Wasowicz, M., Karkouti, K., & Sharma, V. (2015). The role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery: A systematic review and meta-analysis. Anaesthesia, 70(6), 715-731. doi:http://dx.doi.org/10.1111/anae.13083			
Affiliation/Source of funds			
St. George's Hospital, London, UK; Toronto General Hospital, Toronto, Ontario, Canada The authors declared no conflicts of interest or external sources of funding.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs (observational studies not included)	I	Countries of included studies not reported	Surgical (cardiac)
Intervention		**Comparator**	
thromboelastography (TEG) or rotational thromboelastometry (ROTEM) algorithm to guide transfusion (with or without other point-of-care platelet function tests)		Standard of care	
Population characteristics			
Patients undergoing cardiac surgery Shore-Lesserson 1999: high risk cardiac surgery - moderate to high risk of microvascular bleeding (valve replacement, CABG, cardiac reoperation, or thoracic aortic replacement) Royston 2001: high-risk cardiac surgery (transplant, Ross procedure, multiple valve + CABG)			

STUDY DETAILS: Corredor 2015	
Avidan 2004: elective CABG with CPB. Excessive bleeding defined as any patient who continued to bleed excessively (> 100 mL/hour), had no evidence of a haemostatic abnormality or had failed to respond to the treatment. Ak 2009: Elective CABG Westbrook 2009: cardiac surgery, ~10% in each group with urgent presentation. Girdauskas 2010: high risk aortic surgery including urgent and emergency surgery (25 with acute type A dissection) with hypothermic circulatory arrest. Nuttal 2001: abnormal microvascular bleeding after CPB, defined as diffuse oozing with no visible clot at inspection of the operative field performed by the surgeon and the anaesthetist after CBP. Weber 2012: complex cardiothoracic surgery (combined CABG and valve surgery, double or triple valve procedures, aortic surgery or redo surgery) with diffuse bleeding from capillary beds at wound surfaces or intraoperative or postoperative (during the first 24 postoperative hours) blood loss exceeding 250 mL/hour or 50 mL/10 min. Agarwal 2015: Emergency and urgent CABG	
Length of follow-up	**Outcomes measured**
Citations published between database inception and October 2014. Included studies published between 1999 and 2014.	Bleeding after cardiac surgery at follow up Proportion of patients receiving packed RBCs Proportion of patients receiving platelets Mortality
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The overall risk of bias for three included studies (Girdauska 2010; Weber 2012; Agarwal 2014) were judged by the review authors to be high, as they received a rating of high risk on at least one domain. Shore-Lesserson 1999 was judged to be of low risk of bias. The remaining two studies (Avidan 2004, Ak 2009) were judged as having an unclear risk of bias. The domains or reasons that resulted in these assessments were not provided.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**TEG/ROTEM** **n/N (%)** **Mean ± SD**	**SoC** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TEG/ROTEM versus standard of care				
Mortality at longest follow-up N = 749 (6 studies) Shore-Lesserson 1999 Ak 2009 Girdauskas 2010 Royston 2001 Weber 2012 Agarwal 2015 *	NR 5/84	NR 4/81	RR 0.66 (0.31, 1.39)	No significant difference *p* = 0.27 *data from primary study
Proportion of patients receiving packed RBC N = 836 (6 studies) TEG/ROTEM only TEG/ROTEM + PFT *TEG/ROTEM only* Ak 2009	NR NR NR *Log[RR] (SE)* –0.1719 (0.1339)	NR NR NR 	RR 0.86 (0.79, 0.94) 0.88 (0.75, 1.03) 0.84 (0.73, 0.97) 0.84 (0.64, 1.09)	*Favours TEG/ROTEM* *p* = 0.001 No heterogeneity I^2 = 11% (*p* = 0.34) Test for subgroup differences: I^2 = 0% No heterogeneity detected

STUDY DETAILS: Corredor 2015				
Girdauskas 2010	–0.046 (0.0847)		0.96 (0.81, 1.13)	
Shore-Lesserson 1999	–0.3624 (0.1992)		0.70 (0.75, 1.03)	
TEG/ROTEM + PFT				
Agarwal 2015	–0.3425 (0.1303)		0.71 (0.55, 0.92)	
Avidan 2004	–0.0305 (0.136)		0.97 (0.74, 1.27)	
Weber 2012	–0.1543 (0.0647)		0.86 (0.75, 0.97)	
Proportion of patients receiving FFP N = NR (studies NR)	NR	NR	RR 0.42 (0.30, 0.59)	*Favours TEG/ROTEM* $p < 0.00001$ Heterogeneity NR
Platelet transfusions N = NR (NR studies) TEG/ROTEM only TEG/ROTEM + PFT	NR	NR	RR 0.81 (0.55, 1.18) 0.59 (0.44, 0.80) 1.16 (0.73, 1.85)	No significant difference $p = 0.27$ $p = 0.007$, Favours TEG/ROTEM $p = 0.52$, No difference
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Guidelines population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: The systematic review and meta-analysis found that point-of-care platelet function tests can indeed detect platelet dysfunction in the peri-operative setting in cardiac surgical patients. In addition, their incorporation into a blood transfusion management algorithm is associated with reduced blood loss and transfusion requirements. Viscoelastic methods (TEG and ROTEM) alone appear to have limited ability for prediction of blood loss and transfusion requirements after cardiac surgery. This limitation is particularly apparent in patients receiving antiplatelet medications, as conventional viscoelastic methods are unable to detect the effect of antiplatelet medications on platelet function. *List of included studies:* Agarwal 2015, Weber 2012, Girdauskas 2010, Ak 2009, Westbrook 2009, Avidan 2004, Nuttall 2001, Royston 2001, Shore-Lesserson 1999				

CI, confidence interval; ITT, intention-to-treat; MD, mean difference; NR, not reported; PFT, platelet function test; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; RBC, red blood cell; RR, relative risk; SD, standard deviation TEG, thromboelastography

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

STUDY DETAILS: Deppe 2016			
Citation			
Deppe, A. C., Weber, C., Zimmermann, J., Kuhn, E. W., Slottosch, I., Liakopoulos, O. J., Choi, Y. H., & Wahlers, T. (2016). Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: A meta-analysis of 8332 patients. *Journal of Surgical Research*, 203(2), 424-433. doi:http://dx.doi.org/10.1016/j.jss.2016.03.008			
Affiliation/Source of funds			
Author affiliations: University of Cologne, Germany The authors declared no conflicts of interest and reported no funding was received.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs and observational studies	I /III	Countries of included studies not reported	Cardiac (Surgery)

STUDY DETAILS: Deppe 2016				
Intervention		**Comparator**		
Transfusion strategy guided by TEG/ROTEM		Standard of care (transfusion regimen guided by standard laboratory tests)		
Population characteristics				
Patients with excessive bleeding after cardiac surgery Included 17 studies (9 RCTs, 8 observational studies) 29.8% female, 27.2% diabetes, 36.2% hypertension, 20.8% COPD				
Length of follow-up		**Outcomes measured**		
Citations published between 1966 and Dec 31 2014		mortality re-exploration morbidity (acute kidney injury, cerebrovascular accident, thromboembolic events) transfusion requirements blood loss		
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* T he overall risk of bias for included studies was judged by the review authors to be high (assessed with Jadad [RCTs] and Downs and Black score [Coh]). Eleven studies were rated as poor, whereas the remaining six studies were rated as being of good quality. There were concerns with patient selection bias due to significant differences in baseline characteristics of comparator groups.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
POCT versus Standard laboratory tests				
Mortality, all cause N = 5899 (6 RCTs, 5 Coh)	163/NR (5.4)	156/NR (5.7)	OR 0.92 (0.74, 1.16)	No significant difference *p* = 0.5193 Mild heterogeneity I^2 = 14% (*p* = 0.4520)
Morbidity, CVA N = 4054 (2 RCTs, 3 Coh)	12/NR (0.5)	18/NR (1.0)	OR 0.64 (0.31, 1.30)	No significant difference *p* = 0.2841 No significant heterogeneity I^2 = 0% (*p* = 0.1345)
Morbidity, acute kidney injury N = 4263 (3 RCTs, 2 Coh)	142/NR (6.0)	150/NR (7.8)	OR 0.77 (0.61, 0.98)	Favours intervention *p* = 0.0403 No significant heterogeneity I^2 = 0% (*p* = 0.0278)
Morbidity, acute kidney injury N = 380 (RCTs only)	NR	NR	OR 0.54 (0.27, 1.06)	No significant difference *p* = 0.1001 Heterogeneity NR
Morbidity, TE N = 3975 (NR studies)	28/NR (1.3)	51/NR (2.9)	OR 0.44 (0.28, 0.70)	Favours intervention *p* = 0.0006

STUDY DETAILS: Deppe 2016				
				No significant heterogeneity I^2 = 0% (p = 0.0005)
Required transfusion, any N = 5223 (NR studies)	1426/NR (49.6)	1413/NR (60.2)	OR 0.63 (0.56, 0.71) NNT 9.4	Favours intervention p = 0.0001 Mild heterogeneity I^2 = 28% (p < 0.0001)
Required transfusion any N = NR (RCTs only)	NR	NR	OR 0.37 (0.21, 0.68) NNT 5.6	Favours intervention p = 0.0018
RBC transfusion N = 6589 (NR studies)	1763/NR (49.4)	1789/NR (59.2)	OR 0.63 (0.50, 0.78) NNT 9.4	Favours intervention p < 0.0001 Mild heterogeneity I^2 = 50% (p < 0.0001)
FFP transfusion N = 6589 (NR studies)	312/NR (8.7)	724/NR (23.9)	OR 0.31 (0.13, 0.74) NNT 6.6	Favours intervention p = 0.0001 Substantial heterogeneity I^2 = 95% (p < 0.0001)
Platelet transfusion N = 6589 (NR studies)	694/NR (19.5)	655/NR (21.7)	OR 0.62 (0.42, 0.92)	Favours intervention p = 0.0187 Substantial heterogeneity I^2 = 80% (p = 0.0292)
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with few caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions Pooled effects from nine RCTs and eight observational studies demonstrates that POCT-based coagulation management decreases the number of patients with allogeneic blood product exposure. Furthermore, it results in significantly lower re-exploration rates, decreases the incidence of postoperative AKI and thromboembolic events in cardiac surgery patients. Despite these findings, there were no significant differences in mortality or ICU and hospital stay. *List of included studies* RCTs: Ak 2009, Avidan 2004, Girdauskas 2010, Kultufan Turan 2006, Nuttall 2001, Royston 2001, Shore-Lesserson 1999, Weber 2012, Westbrook 2009 Prospective cohort: Sun 2014, Fassel 2013, Spalding 2007 Retrospective cohort: Anderson 2006, Görlinger 2011, Hanke 2012, Rahe-Meyer 2009, Spiess 1995				

AKI, acute kidney injury; CVA, cerebrovascular accident; CI, confidence interval; FFP, fresh frozen plasma; PRBC, packed red blood cells; ITT, intention-to-treat; MD, mean difference; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SD, standard deviation ; TEG, thromboelastography; TE, thromboembolic events

a. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Saner 2016
Citation
Saner, F. H., & Kirchner, C. (2016). Monitoring and Treatment of Coagulation Disorders in End-Stage Liver Disease. Visc Med, 32(4), 241-248. doi:10.1159/000446304

STUDY DETAILS: Saner 2016			
Affiliation/Source of funds			
Details on funding not provided. Author conflicts of interest: FH Saner: CSL Behring - Honoraria from speakers bureau; TEM International - research grant			
Study design	**Level of evidence**	**Location**	**Setting**
Selective literature search and narrative review	III	Countries of included studies not provided Wang 2010: Taiwan De Pietri 2010: Italy Leon-Justel 2015: Spain	End stage liver disease
Intervention		**Comparator**	
TEG and/or ROTEM		Standard of care (standard laboratory tests)	
Population characteristics			
Patients with end stage liver disease Wang 2010: those scheduled for orthotopic liver transplant De Pietri 2010: those scheduled for invasive surgical interventions including laparoscopy, biopsy, resection (INR ≥ 1.8, PLT count ≤ 50/nL) Leon-Justel 2015: Cohort study in 200 patients scheduled for liver transplant before and after implementation of ROTEM-guided protocol Bedreli 2016: Patients with advanced cirrhosis and coagulopathy (INR > 1.5, PLT count ≤ 50/nL)			
Length of follow-up		**Outcomes measured**	
Single database (PubMed). Search dates not provided.		Mortality Transfusion requirements Morbidity	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and *should not be relied on* to provide an accurate and comprehensive summary of the available studies. A comprehensive literature review was not conducted. *Risk of bias of included studies:* Quality assessment was not carried out on included studies.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**TEG and/or ROTEM n/N (%)** **Mean ± SD**	**Standard of care n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
Mortality N = 88 (2 RCTs) Wang 2010 De Pietri 2016 [b]	 NR 8/30 (26.6)	 NR 7/30 (23.3)	 NR NR	No significant difference NR *p* = 0.880 (K-M log-rank)
Survival at 1 year N = 200 (1 Coh) Leon-Justel 2015	79/100 (79)	81/100 (81)		No significant difference *p* = 0.663
RBC transfusion volume, units N = 60 (1 RCT) De Pietri 2016 [b]	Total (median) 6 (1) [c]	Total (median) 8 (2) [c]	Diff	No significant difference *p* = 0.39
RBC transfusion volume, units per patient N = 200 (1 Coh)	Median (IQR)	Median (IQR)	Diff	*Favours ROTEM* *p* < 0.0001

STUDY DETAILS: Saner 2016				
Leon-Justel 2015 [d]	3 (0–5)	5 (2–8)		
FFP transfusion volume, units N = 28 (1 RCT) Wang 2010	mean ± SD (n) 21.5 ± NR (NR)	mean ± SD (n) 12.8 ± SD (NR)		*Favours TEG/ROTEM* NR
FFP transfusion volume, units per patient N = 200 (1 Coh) Leon-Justel 2015 [d]	Median (IQR) 0 (0–0)	Median (IQR) 2 (0–4)	Diff	*Favours ROTEM* *p* < 0.0001
FFP transfusion volume, mL N = 60 (1 RCT) De Pietri 2016 [b] Low risk High risk	Total 4000 0	Total 11050 6500		*Favours TEG/ROTEM* *p* = 0.002 *p* < 0.0001
FFP transfusion volume, mL N = 60 (1 RCT) De Pietri 2016 [b] Low risk High risk	Infused per patient (only FFP) 0 0	Infused per patient (only FFP) 895 ± 129 920 ± 303		*Favours TEG/ROTEM* *p* < 0.0001 *p* = 0.002
FFP transfusion volume, mL N = 60 (1 RCT) De Pietri 2016 [b] Low risk High risk	Infused per patient (receiving FFP+PLT) 1333 ± 585 0	Infused per patient (receiving FFP+PLT) 600 ± 141 950 ± 212		*p* = 0.099 *p* = 0.21
PLT transfusion volume, units N = 60 (1 RCT) De Pietri 2016 [b] Low risk High risk	Total 22 6	Total 28 78		*Favours TEG/ROTEM* *p* = 0.046 *p* = 0.001
PLT transfusion volume, units per patient N = 200 (1 Coh) Leon-Justel 2015 [d]	Median (IQR) 0 (0–1)	Median (IQR) 1 (0–4)	Diff	*Favours ROTEM* *p* < 0.0001
PLT transfusion volume, mL N = 60 (1 RCT) De Pietri 2016 [b] Low risk High risk	Infused per patient (only PLT) 225 ± 35 11 ± 45	Infused per patient (only FFP) 263 ± 57 170 ± 140		*p* = 0.406, No difference *p* < 0.0001, Favours TEG/ROTEM
PLT transfusion volume, mL N = 60 (1 RCT) De Pietri 2016 [b] Low risk High risk	Infused per patient (receiving FFP+PLT) 300 ± 10 0	Infused per patient (receiving FFP+PLT) 300 325 ± 35		*Favours TEG/ROTEM* *p* = 0.048 *NR*
FC transfusion volume, g per patient N = 200 (1 Coh) Leon-Justel 2015 [d]	mean ± SD (n) 1.13 ± 1.44	mean ± SD (n) 0.48 ± 1.28	Diff	*Favours SoC* *p* = 0.001

STUDY DETAILS: Saner 2016				
At least one blood component (FFP, and/or PLT) N = 60 (1 RCT) De Pietri 2016 [b]	5/30 (16.7%)	30/30 (100%)	NR	*Favours TEG/ROTEM* *p* < 0.0001
Transfusion avoided N = 200 (1 Coh) Leon-Justel 2015 [d]	24/100 (24)	5/100 (5)		*Favours TEG/ROTEM* *p* < 0.0001
Need for massive transfusion (> 10U RBCs) N = 200 (1 Coh) Leon-Justel 2015 [d]	2/100 (2)	13/100 (13)		*Favours TEG/ROTEM* *p* = 0.005
RBC transfusion, post procedure N = 60 (1 RCT) De Pietri 2016 [b]	4/30 (13.3)	4/30 (13.3)		No significant difference *p* = 0.718
FFP only N = 60 (1 RCT) De Pietri 2016 [b]	0/30	16/30 (53.3)	NR	*Favours TEG/ROTEM* *p* < 0.0001
PLT only N = 60 (1 RCT) De Pietri 2016 [b]	2/30 (6.7)	10/30 (33.3)	NR	*Favours TEG/ROTEM* *p* = 0.009
Both FFP & PLT N = 60 (1 RCT) De Pietri 2016 [b]	3/30 (10)	4/30 (13.3)	NR	No significant difference NR
Clinically significant bleeding N = 60 (1 RCT) De Pietri 2016 [b]	0/30	1/30 (3.3)		No significant difference *p* = 0.313
Transfusion associated allergic reaction N = 60 (1 RCT) De Pietri 2016 [b]	0/30	1/30 (3.3)		No significant difference *p* = 0.313
Acute kidney injury N = 200 (1 Coh) Leon-Justel 2015	2/100 (2)	17/100 (17)		*Favours ROTEM* *p* = 0.001
Reoperation due to bleeding N = 200 (1 Coh) Leon-Justel 2015	5/100 (5)	13/100 (13)		*Favours ROTEM* *p* = 0.048
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: Coagulation management should be based on VET analysis because this kind of coagulation analysis reflects coagulation dynamics better, enables a faster reaction to an imbalance in the coagulation system, and is the gold standard for detecting fibrinolysis. *List of relevant included studies:*				

STUDY DETAILS: Saner 2016
Wang 2010, De Pietri 2016, Leon-Justel 2015

Coh, cohort; CI, confidence interval; ESLD, end-stage liver disease; FFP. fresh frozen plasma; INR, international normalized ratio; RBC, red blood cells; PCC, prothrombin complex concentrate; PC platelet concentrate; RBC, red blood cell; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; SD, standard deviation; SLT, standard laboratory tests; TEG, thromboelastography; VET, viscoelastic test

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Data sourced from primary study. Low risk procedure defined as bleeding probability lower than 3%, high risk procedure defined as bleeding probability exceeding 3%.

c. related to anaemia not overt bleeding. An additional 2 units related to bleeding episode administered in the SoC group.

d. Data sourced from primary study.

STUDY DETAILS: Wikkelso 2016			
Citation			
Wikkelso, A., Wetterslev, J., Moller, A.M., et al. 2016. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database of Systematic Reviews*, 2016 (8) (no pagination). Wikkelso, A., Wetterslev, J., Moller, A. M., & Afshari, A. (2017). Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. *Anaesthesia*, 72(4), 519-531. doi:http://dx.doi.org/10.1111/anae.13765			
Affiliation/Source of funds			
Supported by Cochrane Anaesthesia, Critical and Emergency Care Review Group (ACE), Denmark. *Author affiliations:* University of Copenhagen, Denmark Conflicts of interest: AW, AA, and MM have received product, but no financial support, from company for an RCT investigating fibrinogen concentrate in postpartum haemorrhage with TEG used as haemostatic monitoring (trial not part of this review); JW is a member of Trial Sequential Analysis (TSA) at Copenhagen Trial Unit developing and programming TSA.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs	Level I	Ak 2009: Turkey Avidan 2004: UK Cui 2010: China Girdauskas 2010: Germany Kempfert 2011: Germany Kultufan Turan 2006: Turkey Nakayama 2015: Japan NCT00772239: France Nuttal 2001: USA Paniagua 2011: Spain Rauter 2007: Austria Royston 2001: UK Schaden 2012: Austria Shore-Lesserson 1999: USA Wang 2010: Taiwan Weber 2012: Germany Westbrook 2009: Australia	Single centre, University hospital/ hospital
Intervention		**Comparator**	
TEG guided transfusion: Ak 2009, Cui 2010, Kultufan Turan 2006, Royston 2001, Shore-Lesserson 1999, Wang 2010 *TEG guided transfusion with platelet function analysis:* Avidan 2004, Westbrook 2009 *TEG guided transfusion with other laboratory tests:* Nuttal 2001		*Clinical judgement or usual treatment:* Ak 2009, Cui 2010, Girdauskas 2010, Kultufan Turan 2006, NCT00772239, Nuttal 2001, Rauter 2007, Royston 2001, Schaden 2012, Shore-Lesserson 1999, Westbrook 2009	

STUDY DETAILS: Wikkelso 2016	
ROTEM guided transfusion: Girdauskas 2010, Kempfert 2011, Nakayama 2015, NCT00772239, Paniagua 2011, Rauter 2007, Schaden 2012 *ROTEM guided transfusion with platelet function analysis:* Weber 2012	*Predefined algorithm based on standard laboratory test-guided transfusion:* Avidan 2004, Kempfert 2011, Nakayama 2015, Paniagua 2011, Wang 2010, Weber 2012
Population characteristics	
Adult patients with bleeding: Ak 2009: elective CABG with CPB; excessive bleeding was defined as mediastinal blood loss over 400 mL in the first hour after surgery or over 100 mL/hour for 4 consecutive hours. Significantly more patients in the TEG group received TXA (10.3% vs 19%, p = 0.007) Avidan 2004: elective CABG with CPB. Excessive bleeding defined as any patient who continued to bleed excessively (> 100 mL/hour), had no evidence of a haemostatic abnormality or had failed to respond to the treatment. Girdauskas 2010: high risk aortic surgery including urgent and emergency surgery (25 with acute type A dissection) with hypothermic circulatory arrest. Kempfert 2011: significant postoperative bleeding (> 200 mL/hour) following standard elective isolated or combined cardiac surgical procedures Kultufan Turan 2006: CABG or valve surgery. Definition of excessive bleeding not stated. NCT00772239: cardiac surgery or heart transplantation with abnormal bleeding. Nuttal 2001: abnormal microvascular bleeding after CPB, defined as diffuse oozing with no visible clot at inspection of the operative field performed by the surgeon and the anaesthetist after CBP. Paniagua 2011: patients undergoing cardiac surgery with excessive or diffuse bleeding after protamine. Excessive bleeding defined as mediastinal chest tube drainage ≥ 300 mL in the first hour after surgery: ≥ 250 mL in the second hour or ≥ 150 mL at any later time. Rauter 2007: elective on-pump cardiac surgery. Definition of excessive bleeding not stated. Royston 2001: cardiac surgery (heart transplantation, revascularization, bypass, Ross procedure, multiple valve or valve and revascularization surgery) Schaden 2012: surgical excision of burn wounds performed on the third day after burn trauma. Bleeding defined as clinically bleeding patient, diffuse bleeding, no visible clot in the operation site, no apparent vascular injury; hemodynamically relevant blood loss requiring additional volume therapy Shore-Lesserson 1999: cardiac surgical patients at moderate to high risk of microvascular bleeding (valve replacement, CABG, cardiac reoperation, or thoracic aortic replacement) Wang 2010: orthotopic liver transplantation Weber 2012: elective, complex cardiothoracic surgery (combined CABG and valve surgery, double or triple valve procedures, aortic surgery or redo surgery) with diffuse bleeding from capillary beds at wound surfaces or intraoperative or postoperative (during the first 24 postoperative hours) blood loss exceeding 250 mL/hour or 50 mL/10 min. Westbrook 2009: cardiac surgery, ~10% in each group with urgent presentation. *Children (aged less than 18 years) with bleeding:* Cui 2010: cyanotic paediatric patients undergoing arterial switch operation or double roots transplantation. Definition of excessive bleeding not stated. Nakayama 2015: elective cardiac surgery with CBP in children less than 20 kg. Diffuse bleeding was an entry criterion for the algorithm, but some of the included patients did not fulfil this criterion.	
Length of follow-up	**Outcomes measured**
Follow-up ranged from 24 hours to three years (Wang 2010), but information on six trials was unclear or did not provide data Literature search updated 5 Jan 2016	Mortality, bleeding events, blood loss, patients receiving transfusion, amount of product transfused, complications, incidence of surgical interventions and reoperation, quality of life, duration of mechanical ventilation, length of stay, cost-benefit,
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. Cochrane review. Protocol first published 2009. Updated 2017.	

STUDY DETAILS: Wikkelso 2016				
Risk of bias of included studies: Only two of seventeen studies were judged to be of low risk of bias. Many of the studies were open label or did not provide information on blinding and had issues with incomplete report of outcome data, short follow-up, and small sample size.				
RESULTS:				
Outcome **No. patients (No. trials)**	**TEG or ROTEM** **n/N (%)** **Mean ± SD**	**Clinical judgement or usual care** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TEG/ROTEM versus any comparator				
Mortality, last follow-up* N = 717 (8 trials) TEG (4 trials) ROTEM (4 trials) *majority (7 out of 8 trials) were at hospital discharge	14/364 (3.9%) 5/211 9/153	26/353 (7.4%) 7/206 19/147	M-H Fixed effect RR 0.52 (0.28, 0.95) Adjusted 0.51 (0.21, 1.26)[b] RR 0.72 (0.25, 2.07) RR 0.44 (0.21, 0.93) *two trials had zero events	*Favours TEG/ROTEM* *p* = 0.033 No heterogeneity I^2 = 0% (*p* = 0.54)
Mortality, last follow-up N = 717 (8 trials)	14/364 (3.9%)	26/353 (7.4%)	M-H Random effects RR 0.57 (0.30, 1.07) Adjusted 0.59 (0.23, 1.54)[b]	No significant difference *p* = 0.08 No heterogeneity I^2 = 0% (*p* = 0.54)
Patients receiving RBC N = 832 (10 trials) TEG (5 trials) ROTEM (5 trials)	261/422 (61.8%) 118/255 143/167	295/410 (72%) 143/247 152/163	RR 0.86 (0.79, 0.94) Adjusted 0.86 (0.79, 0.95) RR 0.80 (0.68, 0.95) RR 0.92 (0.85, 0.99)	*Favours TEG/ROTEM* *p* = 0.001 No heterogeneity I^2 = 0% (*p* = 0.50)
Patients receiving FFP N = 761 (8 trials) TEG (3 trials) ROTEM (5 trials)	108/385 (28%) 25/218 833/167	177/376 (47%) 47/213 130/163	RR 0.57 (0.33, 0.96) RR 0.52 (0.20, 1.35) RR 0.58 (0.30, 1.12)	*Favours TEG/ROTEM* *p* = 0.034 Substantial heterogeneity I^2 = 86% (*p* < 0.00001)
Patients receiving platelets N = 832 (10 trials) TEG (5 trials) ROTEM (5 trials)	106/422 (25.1%) 32/255 74/167	141/410 (34.4%) 50/247 91/163	RR 0.73 (0.60, 0.88) RR 0.61 (0.41, 0.91) RR 0.79 (0.64, 0.98)	*Favours TEG/ROTEM* *p* = 0.0012 No heterogeneity I^2 = 0% (*p* = 0.55)
Patients receiving FFP and platelets N = 165 (2 trials) Royston 2001 Shore-Lesserson 1999	12/83 5/30 7/53	27/82 10/30 17/52	RR 0.44 (0.24, 0.81)	*Favours TEG/ROTEM* *p* = 0.008 No heterogeneity I^2 = 0% (*p* = 0.73)
Patients receiving fibrinogen concentrate N = 156 (2 trials) Girdauskas 2010 Weber 2012	53/77 21/27 32/50	56/79 26/29 30/50	RR 0.94 (0.76, 1.17)	No significant difference *p* = 0.59 Mild heterogeneity I^2 = 22% (*p* = 0.26)
Patients receiving prothrombin complex concentrate N = 156 (2 trials)	26/77	52/79	RR 0.39 (0.07, 2.16)	No significant difference *p* = 0.28 Substantial heterogeneity I^2 = 91% (*p* = 0.00064)

STUDY DETAILS: Wikkelso 2016				
Girdauskas 2010	4/27	26/29		
Weber 2012	22/50	26/50		
Dialysis dependent renal failure N = 200 (3 trials) Girdauskas 2010 Paniagua 2011 Weber 2012	16/103 5/27 8/26 3/50	30/97 7/29 13/18 10/50	RR 0.46 (0.28, 0.76)	*Favours TEG/ROTEM* *p* = 0.0028 No heterogeneity I^2 = 0% (*p* = 0.48)
Thromboembolic events N = 305 (4 trials) Girdauskas 2010 Paniagua 2011 Shore-Lesserson 1999 Weber 2012	5/156 4/27 0/26 1/53 0/50	5/149 3/29 0/18 0/52 2/50	RR 1.04 (0.35, 3.07)	No significant difference *p* = 0.94 No heterogeneity I^2 = 0% (*p* = 0.41)
Excessive bleeding events and massive transfusion N = 280 (2 trials) Ak 2009 Girdauskas 2010	16/141 11/114 5/27	19/139 9/110 10/29	RR 0.82 (0.38, 1.77)	No significant difference *p* = 0.61 Moderate heterogeneity I^2 = 34% (*p* = 0.22)
Continuous outcomes				
RBC transfusion volume, Units Rauter 2007 Schaden 2012 Wang 2010	Mean (SD) 0.8 3.1 (2.1) 14.2 (7.1)	Mean (SD) 1.3 4.8 (3.0) 16.7 (12.8)	SMD [d] NR –0.63 (–1.37, 0.11) –0.23 (–0.98, 0.51)	*p* < 0.05 [c] *p* = 0.12 *p* > 0.05
Ak 2009 Cui 2010 Girdauskas 2010 Kultufan Turan 2006 Weber 2012	Median (IQR) 1 (0, 1) 1 (1, 1) 6 (2, 13) 0 (0, 3) 3 (2, 6)	Median (IQR) 1 (1, 2) 1 (0.7, 1.9) 9 (4, 14) 1 (0, 2) 5 (4, 9)		*p* = 0.599 *p* > 0.05 *p* = 0.20 *p* = 0.100 *p* < 0.001
Nuttal 2001	Median (range) 2 (0, 9)	Median (range) 3 (0, 70)		*p* = 0.039
Westbrook 2009	Total 14	Total 33		*p* = 0.12 [c]
RBC transfusion volume, mL Paniagua 2011 Shore-Lesserson 1999	Mean (SD) 1774 (1394) 354 (487)	Mean (SD) 1604 (1366) 475 (593)	SMD [d] 0.12 (–0.48, 0.72) –0.22 (–0.61, 0.16)	 NR *p* = 0.12
Avidan 2004	Median (IQR) 500 (0, 678)	Median (IQR) 495 (0, 612)		*p* = 0.03
RBC transfusion volume, mL/kg Nakayama 2015	Mean (IQR) 22 (11, 34)	Mean (IQR) 30 (20, 39)		 *p* = 0.02
FFP transfusion volume, Units Kultufan Turan 2006 Shore-Lesserson 1999 Wang 2010	Mean (SD) 2.8 (0.95) 36 (142) 12.8 (7.0)	Mean (SD) 2.7 (1.5) 217 (436) 21.5 (12.7)	SMD d 0.08 (–0.54, 0.70) –0.56 (–0.95, –0.17) –0.82 (–1.60, –0.05)	 *p* = 0.403 *p* < 0.04 *p* < 0.05

STUDY DETAILS: Wikkelso 2016				
	Median (IQR)	Median (IQR)		
Ak 2009	1 (1, 1)	1 (1, 2)		*p* = 0.001
Girdauskas 2010	3 (0, 12)	8 (4, 18)		*p* = 0.01
Schaden 2012	0 (0, 0)	5.0 (1.5, 7.5)		*p* < 0.001
Weber 2012	0 (0, 3)	5 (3, 8)		*p* < 0.001
	Median (range)	Median (range)		
Nuttal 2001	2 (0, 10)	4 (0, 75)		*p* = 0.005
	Total	Total		
Rauter 2007	0	4		NR
Royston 2001	5	16		*p* < 0.05 [c]
Westbrook 2009	22	18		NR
FFP transfusion volume, mL	Mean (SD)	Mean (SD)	SMD d	
Cui 2010	719 (216)	883 (335)	–0.58 (–1.30, 0.14)	*p* < 0.05
Paniangua 2011	799 (1188)	707 (997)	0.08 (–0.52, 0.68)	NR
FFP transfusion volume, mL/kg	Median (IQR)	Median (IQR)		
Nakayama 2015	26 (16, 31)	25 (12, 41)		*p* = 0.87
Platelet transfusion volume, Units	Mean (SD)	Mean (SD)		
Wang 2010	27.5 (13.9)	30.1 (18.5)		*p* > 0.05
	Median (IQR)	Median (IQR)		
Ak 2009	1 (1, 1)	1 (1, 2)		*p* = 0.001
Cui 2010	1 (1, 1)	1 (0.7, 1.9)		*p* > 0.05
Girdauskas 2010	2 (2, 3)	2 (2, 3)		*p* = 0.70
Kultufan Turan 2006	0 (0, 4)	0 (0, 0)		*p* = 0.411
Weber 2012	2 (0, 2)	2 (0, 5)		*p* = 0.010
	Median (range)	Median (range)		
Nuttal 2001	6 (0, 18)	6 (0, 144)		*p* = 0.0001
Schaden 2012	0 (0, 0)	0 (0, 2)		*p* = 0.12
	Total	Total		
Royston 2001	1	9		*p* < 0.05 [c]
Westbrook 2009	5	15		NR
Platelet transfusion volume, mL	Mean (SD)	Mean (SD)		
Paniangua 2011	212 (307)	331 (406)		NR
Shore-Lesserson 1999	34 (94)	83 (160)		*p* = 0.16
Platelet transfusion volume, mL/kg	Median (IQR)	Median (IQR)		
Nakayama 2015	0 (0, 25)	0 (0, 17)		*p* = 0.28
TEG/ROTEM versus clinical judgement or usual treatment (post-hoc analysis)				
Mortality	7/224	9/221	RR 0.81 (0.32, 2.01)	No significant difference
N = 445 (4 trials)				*p* = 0.65
Ak 2009	3/114	2/110	1.45 (0.25, 8.50)	No heterogeneity
Girdauskas 2010	4/27	5/29	0.86 (0.26, 2.87)	I^2 = 0% (*p* = 0.53)
Royston 2001	0/30	0/30	Not estimable	
Shore-Lesserson 1999	0/53	2/52	0.20 (0.01, 3.99)	
Patients receiving RBC	120/245	150/241	RR 0.85 (0.73, 1.00)	No significant difference
N = 486 (6 trials)				*p* = 0.048
Ak 2009	52/114	60/110	0.84 (0.64, 1.09)	Moderate heterogeneity

STUDY DETAILS: Wikkelso 2016				
Cui 2010	3/17	5/14	0.49 (0.14, 1.71)	I^2 = 31% (p = 0.2)
Girdauskas 2010	24/27	27/29	0.95 (0.81, 1.13)	
Kultufan Turan 2006	7/20	12/20	0.58 (0.29, 1.17)	
Schaden 2012	12/14	15/16	0.91 (0.71, 1.17)	
Shore-Lesserson 1999	22/53	31/52	0.70 (0.47, 1.03)	
Patients receiving FFP	32/ 208	86/ 207	0.38 (0.21, 0.68)	*Favours TEG/ROTEM*
N = 415 (4 trials)				p = 0.0012
Ak 2009	19/114	31/110	0.59 (0.36, 0.98)	Substantial heterogeneity
Girdauskas 2010	9/27	25/29	0.39 (0.22, 0.67)	I^2 = 52% (p = 0.10)
Schaden 2012	0/14	14/16	0.04 (0.00, 0.60)	
Shore-Lesserson 1999	4/53	16/52	0.25 (0.09, 0.68)	
Patients receiving platelets	44/245	75/241	RR 0.59 (0.43, 0.80)	*Favours TEG/ROTEM*
				p = 0.00058
N = 486 (6 trials)	17/114	29/110	0.57 (0.33, 0.97)	No heterogeneity
Ak 2009	5/17	5/14	0.82 (0.30, 2.28)	I^2 = 0% (p = 0.72)
Cui 2010	14/27	23/29	0.65 (0.43, 0.98)	
Girdauskas 2010	1/20	0/20	3.00 (0.13, 69.52)	
Kultufan Turan 2006	0/14	3/16	0.16 (0.01, 2.89)	
Schaden 2012	7/53	15/52	0.46 (0.20, 1.03)	
Shore-Lesserson 1999				
TEG/ROTEM] versus standard laboratory test-guided transfusion (post-hoc analysis)				
Mortality	7/140	9/132	RR 0.36 (0.16, 0.84)	*Favours TEG or ROTEM*
N = 272 (4 trials)				p = 0.018
Nakayama 2015	0/50	0/50	Not estimable	No significant heterogeneity
Paniagua 2011	3/26	4/18	0.52 (0.13, 2.05)	
Wang 2010	2/14	3/14	0.67 (0.13, 3.40)	I^2 = 0% (p = 0.49)
Weber 2012	2/50	10/50	0.20 (0.05, 0.87)	
Patients receiving RBC	107/126	110/118	RR 0.91 (0.83, 1.00)	No significant difference
N = 244 (3 trials)				p = 0.041
Nakayama 2015	42/50	45/50	0.93 (0.80, 1.09)	No significant heterogeneity
Paniagua 2011	23/26	16/18	1.00 (0.80, 1.23)	I^2 = 0% (p = 0.44)
Weber 2012	42/50	49/50	0.86 (0.75, 0.97)	
Patients receiving FFP	76/ 177	91/ 169	RR 0.83 (0.49, 1.40)	No significant difference
N = 346 (4 trials)				p = 0.48
Avidan 2004	2/51	0/51	5.00 (0.25, 101.63)	Substantial heterogeneity
Nakayama 2015	42/50	43/50	0.98 (0.83, 1.15)	I^2 = 79% (p = 0.003)
Paniagua 2011	12/26	8/18	1.04 (0.54, 2.01)	
Weber 2012	20/50	40/50	0.50 (0.35, 0.72)	
Patients receiving platelets	60/126	65/118	RR 0.87 (0.68, 1.11)	No significant difference
				p = 0.26
N = 244 (3 trials)	22/50	22/50	1.00 (0.64, 1.56)	No significant heterogeneity
Nakayama 2015	10/26	10/18	0.69 (0.37, 1.31)	I^2 = 0% (p = 0.64)
Paniagua 2011	28/50	33/50	0.85 (0.62, 1.16)	
Weber 2012				
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats The majority of patients were undergoing cardiac surgery with cardiopulmonary bypass. Population included liver transplants (one trial), wound excisions of burn patients (one trial), cardiac surgery patients (96%). Patients had intra- or post-operative bleeding but not all were critical.				

STUDY DETAILS: Wikkelso 2016
Applicability (relevance of the evidence to the Australian health care system)
The evidence is directly applicable to the Australian healthcare context with few caveats. All but two studies conducted in countries with a similar health care system as Australia.
Additional comments
Authors conclusions Low quality evidence suggests application of TEG- or ROTEM- guided transfusion strategies may reduce the need for blood products and improve morbidity in patients with bleeding. Almost all evidence is in elective cardiac surgery involving CPB. *List of included studies (patients with critical bleeding)* The authors identified 17 RCTs that enrolled 1493 participants. *No coagulopathy or severe postoperative bleeding at inclusion:* Ak 2009, Avidan 2004, Cui 2010, Girdauskas 2010, Kultufan Turan 2006, Nakayama 2015, Royston 2001, Schaden 2012, Shore-Lesserson 1999, Wang 2010, Westbrook 2009 *Coagulopathy or severe postoperative bleeding at inclusion:* Kempfert 2011, Nuttal 2001, Paniagua 2011, Weber 2012 Two trials provided no data: NCT00772239; Rauter 2007

CI, confidence interval; ITT, intention-to-treat; MD, mean difference; PP, per-protocol; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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%.

b. Trial sequential analysis showed only 54% of required information size (717/1325) had been reached. Not statistically significant with control event proportion of 7.4%.

c. *p*-value is/appears to be calculated based on units given to each group instead of mean/median, thereby wrongly assuming that each of the units given are independent

d. Calculated posthoc using RevMan 5.4

STUDY DETAILS: Fahrendorff 2017			
Citation			
Fahrendorff, M., Oliveri, R. S., & Johansson, P. I. (2017). The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products - A systematic review and meta-analysis. Scandinavian journal of trauma, resuscitation and emergency medicine, 25(1), 39. doi:http://dx.doi.org/10.1186/s13049-017-0378-9			
Affiliation/Source of funds			
Author affiliations: Section for Transfusion Medicine, Capital Region Blood Bank, Copenhagen; Department of Surgery, Centre for Translational Injury Research, UT Health, University of Texas; Center for Systems Biology. The School of Engineering and Natural Sciences, University of Iceland The authors declared no conflicts of interest and no funding.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs	I	List countries of the included studies not provided Cao 2016 (China)* * article in Chinese	Trauma (Gonzalez 2016) Obstetrics and maternity (Barinov 2015 [PPH]), Burns excision (Schaden 2012) Hepatic surgery (De Pietri 2015) Liver transplant (Wang 2010) Scoliosis (Cao 2016) Cardiothoracic (9 trials)
Intervention		**Comparator**	
VHA-guided algorithm: *TEG:* Ak 2009; Avidan 2004; Barinov 2015; Cao 2016; De Pietri 2015; Gonzalez 2015; Nuttall 2001; Royston 2001; Shore-Lesserson 1999; Wang 2010; Westbrook 2009		*Standard of Care* The clinician's discretion and/or based on conventional coagulation tests	

STUDY DETAILS: Fahrendorff 2017	
ROTEM: Girdauskas 2010; Paniagua 2011; Schaden 2012; Weber 2012	
Population characteristics	
Patients with an acute need for blood products due to bleeding	
Length of follow-up	**Outcomes measured**
Search of PubMed and Embase. Literature search dates not provided. Only RCTs included. Paediatric trials excluded.	Mortality Perioperative bleeding Transfusion requirements (RBC, FFP, PLT)* *Where transfusion volume was reported in mL, the authors calculated the corresponding number of units using the following conversion factors: 1U RBC = 250 mL/U 1U FFP = 270 mL/U 1U PLT = 340 mL/U (based on standard volume over the previous years in the Capital Region Blood Bank, Rigshospitalet, Copenhagen)
INTERNAL VALIDITY	
Overall QUALITY of the systematic review (descriptive)	
Rating (AMSTAR): Low *Description:* One critical flaw with or without non-critical weaknesses – the review has a critical flaw and ***may not*** provide an accurate and comprehensive summary of the available studies that address the question of interest. Search dates were not provided and no quality assessment of the included studies was performed. *Risk of bias of included studies:* The overall risk of bias for included studies was not assessed by the review authors. There was mention that the decision to transfuse potentially encompasses a bias to a greater number of transfusions between clinicians with a different background and clinical practice. The bias is likely to favour the control.	

RESULTS:

Outcome **No. patients** **(No. trials)**	**VHA** **n/N (%)** **Mean ± SD**	**Control** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
VHA versus Control				
Mortality (all cause) N = 579 (6 studies)	30/291 (10.3)	47/288 (16.3)	OR 0.60 (0.34, 1.07)	No significant difference *p* = 0.08 Mild heterogeneity I^2 = 11% (*p* = 0.35)
Ak 2009	3/114	2/110	1.46 (0.24,8.91)	
Wang 2010	2/14	3/14	0.61 (0.09, 4.37)	
Girdauskas 2010	4/27	5/29	0.83 (0-.20, 3.50)	
Weber 2012	2/50	10/50	0.17 (0.03, 0.81)	
Gonzalez 2015	11/56	20/55	0.43 (0.18, 1.01)	
De Pietri 2016	8/30	7/30	1.19 (0.3.85)	
RBC transfusion volume N = 453 (6 studies)	NA (260)	NA (193)	SMD –0.64 (–1.12, –0.15)	*Favours TEG/ROTEM* *p* = 0.01 Substantial heterogeneity I^2 = 82% (*p* = 0.001)
Shore-Lesserson 1999	1.416 ± 1.948 (53)	1.9 ± 2.372 (52)	–0.22 (–0.61, 0.16)	
Wang 2010	14.2 ± 7.1 (14)	16.7 ± 12.8 (14)	–0.23 (–0.98, 0.51)	
Schaden 2012	3.1 ± 2.1 (14)	4.8 ± 3 (16)	–0.63 (–1.37, 0.11)	
Barinov 2015	4.813 ± 1.255 (92)	6.102 ± 2.28 (29)	–0.82 (–1.25, –0.39)	
Gonzalez 2015	13.96 ± 12.68 (55)	15.65 ± 13.85 (54)	–0.13 (–0.59, 0.25)	
Cao 2016	4.5 ± 1.5 (32)	7.1 ± 1.2 (28)	–1.88 (–2.49, –1.26)	

STUDY DETAILS: Fahrendorff 2017				
FFP transfusion volume N = 423 (5 studies)	NA (246)	NA (177)	SMD –1.98 (–3.41, –0.54)	*Favours TEG/ROTEM* *p* = 0.007 Substantial heterogeneity I^2 = 97% (*p* = 0.00001)
Shore-Lesserson 1999	0.133 ± 0.526 (53)	0.804 ± 1.715 (52)	–0.53 (–0.92, –0.14)	
Wang 2010	12.8 ± 7 (14)	21.5 ± 12.7 (14)	–0.82 (–1.60, –0.05)	
Barinov 2015	4.8 ± 1.537 (92)	9.25 ± 1.862 (29)	–2.73 (–3.28, –2.19)	
Gonzalez 2015	7.49 ± 7.37 (55)	7.57 ± 7.86 (54)	–0.01 (–0.39, 0.37)	
Cao 2016	0.867 ± 0.17 (32)	1.904 ± 0.152 (28)	–6.32 (–7.60, –5.05)	
PLT transfusion volume N = 423 (5 studies)	NA (246)	NA (177)	SMD –0.34 (–0.92, 0.24)	No significant difference *p* = 0.25 Substantial heterogeneity I^2 = 87% (*p* = 0.00001)
Shore-Lesserson 1999	0.1 ± 0.276 (53)	0.244 ± 0.471 (52)	–0.37 (–0.76, 0.01)	
Wang 2010	27.3 ± 13.9 (14)	30.1 ± 18.5 (14)	–0.17 (–0.91, 0.58)	
Barinov 2015	1.64 ± 1.95 (55)	1.52 ± 2.15 (54)	0.06 (–0.32, 0.43)	
Gonzalez 2015	1.14 ± 0.6 (92)	0.95 ± 0.72 (29)	0.30 (–0.12, 0.72)	
Cao 2016	2.5 ± 1.3 (32)	4.2 ± 0.6 (28)	–1.62 (–2.21, –1.03)	
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with few caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: Total bleeding volume and the amount of transfused RBCs and FFP was significantly reduced in the VHA-guided intervention groups compared to conventional coagulation tests control group. The difference in RBC requirements may be explained by a better haemostatic competence in TEG/ROTEM-guided groups accomplished through timely administration of plasma and platelets, further supported by the reduction of bleeding in the VHA-guided group of patients. No statistically significant difference was found between groups regarding all cause-mortality and requirement for platelet transfusion. The sizes of the respective trial populations were small and a lack of cohesion in permission of platelet inhibitors, anticoagulants, antifibrinolytics and triggers used to guide resuscitation with blood products was observed. The control groups were managed either by clinical judgement combined with conventional coagulation tests or by the sole use of algorithms applying only conventional coagulation test-triggers for transfusion. *List of included studies* *Cardiac:* Ak 2009, Avidan 2004, Girdauskas 2010, Nuttall 2001, Paniagua 2011, Royston 2001, Shore-Lesserson 1999, Weber 2012, Westbrook 2009 *Other:* Barinov 2015 (PPH), Cao 2016 (scoliosis), De Pietri 2015 (hepatic), Gonzalez 2015 (trauma), Schaden 2012 (burn wounds), Wang 2010 (liver)				

CI, confidence interval; FFP, fresh frozen plasma; OR, odds ratio; PLT, platelet; RBC, red blood cell; PPH, postpartum haemorrhage; RCT, randomised controlled trial; RR, relative risk; ROTEM, rotational thromboelastometry; SD, standard deviation; SMD, standard mean difference; VHA, viscoelastic haemostatic assay;

a. Only applicable to Level I studies with formal meta-analysis. 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%.

STUDY DETAILS: Serraino 2017
Citation
Serraino, G. F., & Murphy, G. J. (2017). Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: Updated systematic review and meta-analysis. British Journal of Anaesthesia, 118(6), 823-833. doi:http://dx.doi.org/10.1093/bja/aex100
Affiliation/Source of funds
The study was funded by British Heart Foundation [RG/13/6/29947 (G.J.M.), CH/12/1/29419 (G.J.M.), and PG/11/95/29173 (G.J.M.)]; Leicester National Institute for Health Research Cardiovascular Biomedical Research Unit (G.J.M.). *Author affiliations:* University of Leicester

STUDY DETAILS: Serraino 2017			
The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of RCTs	I	Countries of included studies not reported	Surgical (cardiac)
Intervention		**Comparator**	
ROTEM, TEG or Sonoclot, alone or combined with Platelet Function analyser		Clinical judgement and standard laboratory tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time, and plasma fibrinogen concentrations.	
Population characteristics			
Mixed cardiac surgery in adult and paediatric patients Karkouti 2016: Mixed cardiac surgery (ROTEM) * * Effective sample size recalculated by Serraino 2017 to account for stepped wedge cluster trial design using the intracluster coefficient calculation of 0.095 as recommended in the Cochrane Handbook ** all other studies previously extracted in Wikkelso 2016			
Length of follow-up		**Outcomes measured**	
Citations published between database inception and December 3, 2016.		Mortality Morbidity including reoperation Resource use: Red Blood Cell, Fresh frozen Plasma and Plasma Transfusion Intensive Care Unit and hospital Length of Stay	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): High *Description:* No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* The overall risk of bias for included studies was judged by the review authors to be high. The risk of procedural bias was high, as there was little or no allocation concealment or blinding of personnel. There were concerns with patient selection bias due to significant differences in baseline characteristics of comparator groups and attrition bias due to incomplete reporting of outcome data, with no explanations given for missing data. The bias is likely to favour the intervention. The trial by Karkouti 2016 was at low risk of bias for all of the conventional bias domains for cluster randomized trials, with the exception of potential funding bias, and also did not demonstrate benefits for important clinical end points.			
RESULTS:			

Outcome **No. patients** **(No. trials)**	**TEG or ROTEM** **n/N (%)** **Mean ± SD**	**Standard of care** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TEG/ROTEM versus standard of care				
Mortality N = 689 (7 trials) Shore-Lesserson 1999 Royston 2001 Ak 2009 Girdauskas 2010 Paniagua 2011 Weber 2012 Nakayama 2014	12/350 (3.4) * see Wikkelso 2016 for individual trial data	23/339 (6.8)	RR 0.55 (0.28, 1.10)	No significant difference *p* = 0.09 No significant heterogeneity I^2 = 1% (*p* = 0.40)
Morbidity, acute kidney injury N = 424 (4 trials) Ak 2009	23/217 (10.6) 7/114	39/207 (18.8) 9/110	RR 0.42 (0.20, 0.86)	*Favours TEG/ROTEM* *p* = 0.02 Mild heterogeneity I^2 = 26% (*p* = 0.25)

STUDY DETAILS: Serraino 2017				
Girdauskas 2010 Paniagua 2011 Weber 2012	* see Wikkelso 2016 for individual trial data			
Morbidity, cerebrovascular accident N = 163 (2 trials) Girdauskas 2010 Shore-Lesserson 1999	5/80 (6.3) * see Wikkelso 2016 for individual trial data	3/81 (3.7)	RR 1.73 (0.41, 7.23)	No significant difference *p* = 0.45 No heterogeneity I^2 = 0% (*p* = 0.68)
Morbidity, time on ventilation (hrs) N = 328 (3 trials) Ak 2009 Girdauskas 2010 Paniagua 2011	NR	NR	MD 0.28 (–0 .66, 1.23)	No significant difference *p* = 0.56 No heterogeneity I^2 = 0% (*p* = 0.49)
RBC transfusion N = 1116 (11 trials) Karkouti 2016 Westbrook 2009 Ak 2009 Avidan 2004 Cui 2010 Girdauskas 2010 Kultufan Turan 2006 Nakayama 2014 Paniagua 2011 Shore-Lesserson 1999 Weber 2012	321/567 (56.6%) 58/127 14/32 * see Wikkelso 2016 for individual trial data	365/549 (66.5%) 52/118 33/37	RR 0.88 (0.79, 0.97) RR 1.04 (0.78, 1.37) RR 0.49 (0.33, 0.74)	*Favours TEG/ROTEM* *p* = 0.01 Moderate heterogeneity I^2 = 43% (*p* = 0.06)
FFP transfusion [b] N = 976 (8 trials) Karkouti 2016 Ak 2009 Avidan 2004 Girdauskas 2010 Nakayama 2014 Paniagua 2011 Shore-Lesserson 1999 Weber 2012	138/498 (27.7%) 30/127 * see Wikkelso 2016 for individual trial data	187/478 (39.1%) 24/118	RR 0.68 (0.46, 1.00) RR 1.16 (0.72, 1.87)	*Favours TEG/ROTEM* *p* = 0.05 Substantial heterogeneity I^2 = 79% (*p* = 0.0001)
Platelet transfusion [b] N = 1047 (10 trials) Karkouti 2016 Ak 2009 Avidan 2004 Cui 2010 Girdauskas 2010 Kultufan Turan 2006 Nakayama 2014 Paniagua 2011	137/535 (NR) 31/127 * see Wikkelso 2016 for individual trial data	169/512 (NR) 31/118	RR 0.78 (0.66, 0.93) RR 1.16 (0.72, 1.87)	*Favours TEG/ROTEM* *p* = 0.004 No heterogeneity I^2 = 0% (*p* = 0.60)

STUDY DETAILS: Serraino 2017				
Shore-Lesserson 1999 Weber 2012				
Fibrinogen concentrate N = NR (2 trials) Girdauskas 2010 Weber 2012	53/77 (68.8) * see Wikkelso 2016 for individual trial data	56/79 (70.9)	RR 0.94 (0.76, 1.17)	No significant difference *p* = 0.59 Mild heterogeneity I^2 = 22% (*p* = 0.26)
Prothrombin complex concentrate N = NR (2 trials) Girdauskas 2010 Weber 2012	26/77(NR) * see Wikkelso 2016 for individual trial data	56/79 (NR)	RR 0.39 (0.07, 2.16)	No significant difference *p* = 0.28 Substantial heterogeneity I^2 = 91% (*p* = 0.0006)
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with few caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats				
Additional comments				
Authors conclusions Evidence to support routine use of viscoelastic testing in cardiac surgery is weak. Authors of the recent Cochrane review stated that further large pragmatic trials at low risk of bias were required to resolve this knowledge gap. However, inclusion of the large pragmatic trial of viscoelastic testing by Karkouti and colleagues did not alter the precision of the estimates from existing parallel group trials. These findings lead us to hypothesize that viscoelastic testing lacks clinical effectiveness. This hypothesis is supported by weak evidence of predictive accuracy of viscoelastic testing for coagulopathic bleeding. On the basis of the weight of the available evidence, further large trials are unlikely to demonstrate clinical benefits for current viscoelastic point-of-care tests. Research should now focus on development of new techniques to identify important and treatable causes of coagulopathy in cardiac surgery. *List of included studies* Karkouti 2016, Nakayama 2015, Weber 2012, Cui 2010, Girdauskas 2010, Paniagua 2011, Ak 2009, Westbrook 2009, Avidan 2004, Nuttall 2001, Royston 2001, Shore-Lesserson 1999 *Notes:* No Sonoclot trials were included. Two trials (NCT00772239; NCT01218074) were published only as protocols without any data available.				

CI, confidence interval; ; FFP, fresh frozen plasma; RBC, red blood cell; MD, mean difference; PP, per-protocol; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; RR, relative risk; SD, standard deviation; TEG, thromboelastography

a. Only applicable to Level I studies with formal meta-analysis. 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%.

b. Numbers differ from that reported in Wikkelso 2016 & 2017. Upon further inspection, Forest plots C and D in Figure 2 are labelled incorrectly (FFP and Platelets switched). Numbers in the text are correct.

STUDY DETAILS: Roullet 2018			
Citation			
Roullet, S., de Maistre, E., Ickx, B., Blais, N., Susen, S., Faraoni, D., Garrigue, D., Bonhomme, F., Godier, A., & Lasne, D. (2018). Position of the French Working Group on Perioperative Haemostasis (GIHP) on viscoelastic tests: What role for which indication in bleeding situations? Anaesthesia Critical Care and Pain Medicine. https://doi.org/10.1016/j.accpm.2017.12.014			
Affiliation/Source of funds			
Details on funding not provided. *Author affiliations:* French Working Group on Perioperative Haemostasis (GIHP) on viscoelastic tests The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Guidelines	I /III	France Mallaiah 2015: UK	Emergency and perioperative

STUDY DETAILS: Roullet 2018			
Review and narrative commentary of available evidence		Snegovskikh 2018: US	
Intervention		**Comparator**	
TEG®, thromboelastography: Kashuk 2012, Johansson 2013, Gonzalez 2015, Wang 2012 *ROTEM®, thromboelastometry* Schöchl 2010, Mallaiah 2015		Any (details not reported)	
Population characteristics			
Patients referred to the following clinical situations: trauma, obstetrics, surgical (cardiac, liver) Gonzalez 2015: Trauma (not specified) Mallaiah 2015: use of a ROTEM-based algorithm for major obstetric haemorrhage (estimated blood loss > 1500 ml) associated with coagulopathy (FIBTEM A5 <12 mm, indicative of a plasma fibrinogen level of 2 g/L) before and after protocol to manage use of fibrinogen concentrate Snegovskikh 2018: prospective cohort use of a ROTEM-based algorithm for PPH management (US) Wikkelsø 2016: Cochrane review involving 17 (mainly cardiac) studies. Karkouti 2016: (12 Canadian centres, 7402 patients) was conducted in two stages: initially no monitoring, then use of ROTEM with an algorithm using EXTEM CT and A10 and FIBTEM A10, and PlateletWorks (Helena Laboratories, Beaumont, Texas, USA). Nakayama 2015: (Paediatrics) compared efficacy of a transfusion algorithm using ROTEM to an approach based on routine tests Wang 2012: not described Roullet 2015: prospective before/after study (conventional strategy vs. ROTEM-guided strategy)			
Length of follow-up		**Outcomes measured**	
Literature search details not provided.		Questions asked: Can viscoelastic tests be used to - identify abnormal haemostasis? - monitor fibrolysis? - guide treatment of coagulopathy? - improve prognosis? - are results obtained more rapidly than laboratory tests? - and should they be at the bedside or the laboratory?	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. Details regarding Study design, study identification, study selection, or critical appraisal of studies not provided. *Risk of bias of included studies:* the risk of bias of included studies were not assessed/reported by the review authors.			
RESULTS:			
Outcome **No. patients** **(No. trials)**	**TEG or ROTEM** **n/N (%)** **Mean ± SD**	**no TEG or ROTEM** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
Trauma				
Mortality N = NR (1 RCT) Gonzalez 2015	Mortality at 28 days was reduced in the group whose management was guided by TEG, with a decrease in deaths occurring mainly in the first 6 hrs.			*Favours intervention* NR

STUDY DETAILS: Roullet 2018				
Transfusion volumes N = NR (1 RCT) Gonzalez 2015	Transfused amounts of RBC, FFP and platelets were comparable. The group receiving the routine tests received more platelets and FFP early compared to the TEG group. At 24 hrs, only the amount of fibrinogen administered was different, being higher in the group managed with routine tests.			No significant difference NR
Several "before-after" cohort studies (Kashuk 2012, Johansson 2013, Schöchl 2010) concluded that the inclusion of viscoelastic tests in mass transfusion protocols could improve the prognosis of patients or reduce transfusion needs. However, their methodology does not allow conclusions to be drawn about the value of viscoelastic tests, as they evaluated the implementation of a protocol including viscoelastic test with no protocol or historical or scoring data.				
Obstetrics and maternity (Postpartum haemorrhage) [b]				
Mortality N = 93 (1 Coh) Mallaiah 2015	0/51	0/42	NR	No significant difference *p* = 0.1211
TRALI N = 93 (1 Coh) Mallaiah 2015	0/51	0/42	NR	No significant difference NR
TACO N = 93 (1 Coh) Mallaiah 2015	0/51	4/42	NR	*Favours ROTEM* *p* = 0.0367
Postpartum hysterectomy N = 179 (2 studies) Mallaiah 2015 Snegovskikh 2018	NR 3/51 (6) 7/28 (25)	NR 6/42 (14) 31/58 (53.5)	NR	No significant difference NR *p* = 0.013
ICU admission N = 179 (2 studies) Mallaiah 2015 Snegovskikh 2018	NR 1/51 (2) 1/28 (3.6)	NR 4/42 (9) 25/58 (43.1)	NR	 No difference, NR *Favours ROTEM, p* < 0.0001
Transfusion volume, any blood product N = 93 (1 Coh) Mallaiah 2015	NR (51)	NR (42)	Data shown in graphs	*Favours ROTEM* *p* = 0.0004
RBC transfusion volume, Units N = 93 (1 Coh) Mallaiah 2015	NR (51)	NR (42)	Data shown in graphs	No significant difference *p* = 0.1211
FFP transfusion volume, Units N = 93 (1 Coh) Mallaiah 2015	NR (51)	NR (42)	Data shown in graphs	*Favours ROTEM* *p* < 0.0001
CRYO transfusion volume, Units N = 93 (1 Coh) Mallaiah 2015	NR (51)	NR (42)	Data shown in graphs	*Favours ROTEM* *p* < 0.0001
PLT transfusion volume, g N = 93 (1 Coh) Mallaiah 2015	NR (51)	NR (42)	Data shown in graphs	*Favours ROTEM* *p* = 0.0035
FC transfusion volume, g N = NR (1 Coh)	NR (51)	NR (42)	Data shown in graphs	*Favours ROTEM* *p* = 0.0005

STUDY DETAILS: Roullet 2018				
Mallaiah 2015				
RBC transfusion received, ≥ 1 Unit N = 86 (1 Coh) Snegovskikh 2018	17/28 (60.7)	55/58 (94.8)	NR	*Favours ROTEM* *p* < 0.001
RBC transfusion received, ≥ 6 Units N = 93 (1 Coh) Mallaiah 2015	5/51 (10)	12/42 (29)	NR	*Favours ROTEM* *p* = 0.0299
FFP transfusion received, ≥ 1 Unit N = 86 (1 Coh) Snegovskikh 2018	3/28 (10.7)	42/58 (72.4)	NR	*Favours ROTEM* *p* < 0.001
CRYO transfusion received, ≥ 5 Units N = 86 (1 Coh) Snegovskikh 2018	6/28 (21.4)	11/58 (19)	NR	No significant difference *p* = 0.78
PLT transfusion received, ≥ 5 Units N = 86 (1 Coh) Snegovskikh 2018	0/28 (0)	26/58 (44.8)	NR	*Favours ROTEM* *p* < 0.001
Received a fibrinogen product N = 93 (1 Coh) Mallaiah 2015	21/51 (41.2)	30/42 (71.4)	NR	*Favours ROTEM* *p* = 0.0062
Est. total blood loss, mL N = 86 (1 Coh) Snegovskikh 2018	Median (IQR) 2000 (1600–2500)	Median (IQR) 3000 (2000–4000)	NR	*Favours ROTEM* *p* < 0.001
Surgical (cardiac)				
Mortality N = 1493 (17 studies) Wikkelsø 2016 * trials using ROTEM only **compared to SLT guided algorithms	NR	NR	RR 0.52 (0.28, 0.95) RR 0.44 0.21, 0.93) RR 0.36 (0.16, 0.84)	*Favours TEG/ROTEM* ***NR***
RBC transfusions N = 1493 (17 studies) Wikkelsø 2016 N = 7402 (1 study) Karkouti 2016 N = NR (1 study) Nakayama 2015	NR NR NR	NR NR NR	RR 0.86 (0.79, 0.94) RR 0.91 (0.85, 0.98) NR	*Reduction* *p* = 0.02. *Favours TEG/ROTEM* Reduction
FFP N = 1493 (17 studies) Wikkelsø 2016 N = 7402 (1 study) Karkouti 2016 N = NR (1 study) Nakayama 2015	NR NR NR	NR NR NR	RR 0.57 (0.33, 0.96) NR NR	Reduction No reduction Reduction (postoperative) Increased (intraoperative)
Platelets				

STUDY DETAILS: Roullet 2018				
N = 1493 (17 studies) Wikkelsø 2016 N = 7402 (1 study) Karkouti 2016 N = NR (1 study) Nakayama 2015	NR NR NR	NR NR NR	RR 0.73 (0.60, 0.88) RR 0.77 (0.68, 0.87) NR	Reduction *p* < 0.001 *Favours TEG/ROTEM* Increased (intraoperative)
Factor concentrates (fibrinogen, CRYO and PCC) N = 7402 (1 study) Karkouti 2016	NR	NR	NR	No reduction
Acute kidney injury N = NR (1 SR) Wikkelsø 2016	NR	NR	RR 0.46 (0.28, 0.76)	Reduction
The results demonstrate the benefit of blood transfusion strategies, possibly combined with a functional platelet test, but with a low level of evidence (heterogeneity of studies, low numbers of patients). It is difficult to distinguish the impact of viscoelastic tests from that of a systematic approach with a defined algorithm of the indication for transfusion. However, these studies suggest that the indication for transfusion based on real-time biological monitoring and a defined algorithm is associated with decreased transfusion and haemorrhagic complications.				
Surgical (liver transplant)				
Transfusion needs N = 60 (1 study) Roullet 2015	NR	NR	NR	No difference * only platelets and fibrinogen guided by ROTEM (not FFP)
FFP N = NR (1 RCT) Wang 2012	NR	NR	NR	Reduction
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context				
Additional comments				
Authors conclusions: The authors concluded that viscoelastic tests *must* be included in algorithms for the management of coagulopathy and bleeding, defined in each centre and for each population of patients. While their value in the management of trauma and in cardiac surgery seems clear, studies with a high level of evidence are still lacking in obstetrics, liver transplantation and paediatrics. The GIHP proposes that viscoelastic tests be included in ACT algorithms, so that labile blood products and factor concentrates may be given based on pre-established thresholds. Prospective multicentric studies evaluating these algorithms are necessary. These diagnostic algorithms for coagulopathy must be part of a comprehensive approach to the management of severe trauma patients in which the main objective is to treat the cause of the bleeding. The GIHP proposes that the fibrinogen concentration should be rapidly evaluated in the event of PPH and viscoelastic tests may be useful in this regard. Given the limitations of viscoelastic tests in evaluating fibrinolytic activity, it is proposed not to guide the administration of tranexamic acid on viscoelastic tests but to administer it as soon as possible in the event of PPH. In cardiac surgery, the GIHP proposes that viscoelastic tests should be used in the event of haemorrhage at the end of surgery and postoperatively. They are carried out essentially at the end of ECC, rather after the neutralisation of heparin, to guide the therapeutic strategy. The recommendation is that they should be included in algorithms. In the case of liver transplants, viscoelastic tests can be an aid in LT by limiting the transfusion of labile blood products, probably at the cost of an increase in the transfusion of fibrinogen. viscoelastic tests lack sensitivity for the diagnosis of hyper fibrinolysis. The GIHP proposes not waiting for the appearance of typical hyper fibrinolysis plots to use antifibrinolytics if other clinical features are present such as diffuse or massive bleeding.				

STUDY DETAILS: Roullet 2018
List of relevant included studies:
SRs: Veigas 2016, Wikkelsø 2016
RCTs: Gonzalez 2015, Snegovskikh 2018, Mallaiah 2015, Karkouti 2016, Nakayama 2015, Wang 2012
Coh: Roullet 2015

ACT, activated clotting time; CI, confidence interval; FFP, fresh frozen plasma; GIHP, French Working Group on Perioperative haemostasis; hrs, hours; ITT, intention-to-treat; LT, liver transplantation; ECC, extracorporeal circulation; MD, mean difference; NR, not reported; PPH, postpartum haemorrhage; PCC, Prothrombin Complex Concentrate; postpartum haemorrhage; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SLT, standard laboratory testing; TEG, thromboelastography; ROTEM, thromboelastometry; USA, United States of America

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Data retrieved from primary studies

STUDY DETAILS: Li 2019			
Citation			
Li, C., Zhao, Q., Yang, K., Jiang, L., & Yu, J. (2019). Thromboelastography or rotational thromboelastometry for bleeding management in adults undergoing cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. Journal of Thoracic Disease, 11(4), 1170-1181. doi:10.21037/jtd.2019.04.39			
Affiliation/Source of funds			
Funding: This meta-analysis was supported by National Natural Science Foundation of China (NSFC-81670385 to J Yu); Foundation of Lanzhou University Second Hospital (ynbskyjj2015-2-1 to J Yu) and Cuiying Technology Innovation Project of Lanzhou University Second Hospital (CY2018-MS05 to Q Zhao) *Author affiliations:* The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location** [a]	**Setting** [a]
Systematic review and meta-analysis of RCTs and observational studies	I-III	Kuiper 2019 (The Netherlands) St-Onge 2018 (Canada)	Cardiac (Kuiper 2019, St-Onge 2018)
Intervention		**Comparator** [a]	
Rotational thromboelastometry (ROTEM)-guided transfusion algorithms (TEM International GmbH, Munich Germany)		Kuiper 2019: Classical guided transfusion algorithm, according to standard laboratory tests, managed via a team approach and activated clotting times using a point of care (POC) device St-Onge 2018: "transfusions on the basis of clinical judgement and standard coagulation test results."	
Population characteristics [a]			
Li 2019: Cardiac surgery patients Kuiper 2019: A single centre, prospective, registry before-and-after study cohort study. All patients undergoing cardiac surgery (CPB) in the respective periods formed part of the study cohort. St-Onge 2018: A single centre retrospective, before-and-after cohort study. All consecutive patients who underwent aortic procedures involving the root, ascending aorta, or aortic arch in the period before and after the implementation of a ROTEM-based transfusion algorithm. Massive transfusion was defined as more than 20 U of allogenic blood products.			
Length of follow-up		**Outcomes measured**	
Citations published between 1980 to August 1, 2017. Searched the Cochrane Register of Controlled Trials, MEDLINE, EMBASE, BIOSIS, International Web of Science, Latin American Caribbean Health Sciences Literature, The Chinese Biomedical Literature Database, Advanced Google, and Cumulative Index to Nursing & Allied Health Literature. Length of follow up:		All-cause mortality (longest follow-up data from each trial regardless of the period of follow-up); Blood loss including mediastinal drainage and post-operative bleeding; Proportion of patients transfused with allogeneic blood products, including red blood cell (RBC) concentrates, fresh frozen plasma (FFP), platelet (PLT) concentrates, CRYO and some pharmacological agents such as fibrinogen concentrate and prothrombin complex concentrate (PCC);	

STUDY DETAILS: Li 2019	
Kuiper 2019: hospital discharge/30d as latest follow-up (6 SoC and 10 ROTEM patients lost to follow up after 30 days) St-Onge 2018: not specified	Incidence of massive bleeding or massive transfusion and surgical re-exploration; Short-term hospitalization outcomes, including length of hospital stay and intensive care unit (ICU) stay.

INTERNAL VALIDITY

Overall QUALITY of the systematic review (descriptive)

Rating (AMSTAR): Moderate

Description: More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review.

No reference is made to a protocol, a priori design or pre-specified methods. Full list of excluded studies not provided and there is no mention of funding sources of the included studies.

Risk of bias of included studies: The overall risk of bias for included studies was judged by the review authors to be unclear or high. Noting that findings and interpretations in this review are limited by the quality and quantity of the available evidence. On one hand, even excluding retrospective and observational studies, most RCTs also have little or no allocation concealment or blinding of clinical personnel, which contributed to the high procedural bias in these trials. Furthermore, control groups in almost all trials had no standard transfusion protocols, random sequence generation, allocation concealment, or blinding. Publication bias are also high for blood loss, FFP transfusion and PLT transfusion.

RESULTS:

Outcome **No. patients** **(No. trials)**	**ROTEM** **n/N (%)** **Mean ± SD (n)**	**Standard of Care** **n/N (%)** **Mean ± SD (n)**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
Mortality (latest follow-up) N = NR (5 RCTs, 3 Coh)	132/2680 (5)	124/2293 (5.4)	RR 0.83 (0.53, 1.30)	No significant difference *p* = 0.4 Moderate heterogeneity I^2 = 25%
RCTs only	12/270 (4.4)	23/259 (8.9)	RR 0.5 (0.26, 0.96)	
St-Onge 2018	7/112 (6.3)	4/112 (3.6)	RR 1.75 (0.53, 5.81)	No difference, *p* = 0.35
Kuiper 2019 * CABG subgroup *propensity-score matched cohort	4/101 (4.0) 0/96 (0)	7 /101 (6.9) 2/72 (2.7)	RR 0.57 (0.17, 1.89)	*p* = 0.537 *p* = 0.185
Massive bleeding [b] or need for massive transfusion [c] N = 5755 (7 studies)	141/3149 (4.5)	172/2606 (6.6)	RR 0.71 (0.54, 0.93)	*Favours intervention* *p* = 0.01 Moderate heterogeneity I^2 = 32%
Ak 2009				
Fassl 2013	19/155 (13)	12/41 (26)	RR 0.42 (0.22, 0.79)	
Karkouti 2016	853/3847	920/3555	RR 0.86 (0.79, 0.93)	
Spiess 1995	56/591 (9.5)	50/488 (10.2)	RR 0.92 (0.64, 1.33)	
Girdauskas 2010				
Görlinger 2011	27/2147 (1.26)	43/1718 (2.5)	RR 0.50 (0.31, 0.81)	
St-Onge 2018	12/112 (11)	23/112 (20.5)	RR 0.52 (0.27, 1.00)	
RBC transfusion volume, Units	Median [IQR] (n)	Median [IQR] (n)		*Favours intervention*
Kuiper 2019 [d]	0 [0, 1] (101)	0 [0, 2] (101)		*p* = 0.003
St-Onge 2018	0 [0, 2] (112)	1 [0, 4] (112)		*p* = 0.03
Kuiper 2019 (N = 202)	Mean (min-max) 0.6 (0, 8)	Mean (min-max) 1.8 (0, 19)		

STUDY DETAILS: Li 2019				
FFP transfusion volume, Units Kuiper 2019 [d] St-Onge 2018 Kuiper 2019 (N = 202)	Median [IQR] (n) 0 [0, 0] (101) 0 [0,2] (112) Mean (min-max) 0.3 (0, 6)	Median [IQR] (n) 0 [0, 0] (101) 0 [0,4] (112) Mean (min-max) 0.8 (0, 14)		*Favours intervention* *p* = 0.031 *p* = 0.04
PLT transfusion volume, Units Kuiper 2019 [d] St-Onge 2018 Kuiper 2019 (N = 202)	Median [IQR] 0 (0, 0) (101) 0 [0, 10] (112) Mean (min-max) 0 (0, 3)	Median [IQR] 0 (0, 0) (101) 5 [0, 10] (112) Mean (min-max) 0 (0, 6)		No significant difference *p* = 0.676 *p* = 0.48
RBC transfusion incidence N = NR (14 studies) RCTs only Kuiper 2019 (24 hr) St Onge 2018	NR/NR 39/101 (38.6) 51/112 (45.5)	NR/NR 56/101 (55.4) 64/112 (57.1)	RR 0.87 (0.83, 0.91) RR 0.89 (0.80, 0.98)	*Favours intervention* *p* < 0.01 Mild heterogeneity I^2 = 11% *Favours intervention* p = 0.024 No difference *p* = 0.08
FFP transfusion incidence N = NR (14 studies) RCTs only Kuiper 2019 (24 hr) St Onge 2018	NR/NR 7/101 (6.9) 32/112 (28.6)	NR/NR 19/101 (18.8) 43/112 (38.4)	RR 0.5 (0.31, 0.80) RR 0.59 (0.42, 0.82)	*Favours intervention* *p* < 0.01 Substantial heterogeneity I^2 = 93% *Favours intervention p = 0.019* *No difference p = 0.12*
PLT transfusion incidence N = NR (14 studies) RCTs only Kuiper 2019 (24 hr) St Onge 2018	NR/NR 20/101 (19.8) 54/112 (48.2)	NR/NR 16/101 (15.8) 61/112 (54.5)	RR 0.86 (0.73, 1.02) RR 0.81 (0.74, 0.90)[e]	No significant difference *p* = 0.08 Substantial heterogeneity I^2 = 62% No difference *p* = 0.582 No difference *p* = 0.35
Cryoprecipitate transfusion incidence St-Onge 2018	 29/112 (25.9)	 31/112 (27.7)		No significant difference *p* = 0.76
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: The authors found that the mortality rate in the TEG/ROTEM group was lower than that in control group, but without statistically significant difference, either in overall studies or in RCTs. The authors found a statistically significant reduction of blood loss in favour of the TEG/ROTEM-guided algorithm in both overall studies and RCTs				

STUDY DETAILS: Li 2019
The use of a TEG/ROTEM-guided algorithm had a significant beneficial effect on the transfusion requirements of RBC and FFP. Though their analysis showed consistent benefits of viscoelastic testing on blood loss and transfusion rates, it failed to reach the same beneficial effects on patients' outcome including mortality, length of hospital stay and ICU stay, even rates of re-exploration and massive bleeding/transfusion.
List of included studies RCTs: Ak 2009, Avidan 2004, Girdauskas 2010, Karkouti 2016, Kempfert 2011, Kultufan Turan 2006, Nuttall 2001, Paniagua 2011, Rauter 2007, Royston 2001, Shore-Lesserson 1999, Weber 2012, Westbrook 2009 Propsective cohort - Kuiper 2019, Retrospective Cohort - Anderson 2006, Görlinger 2011, Spiess 1995, St-Onge 2018 Matched Case Control - Fassl 2013

CPB, cardiac surgery; CI, confidence interval; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IQR, interquartile range; MD, mean difference; NR, not reported; PCC, prothrombin complex concentrate; PP, per-protocol; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; TC, thrombocyte complex

a. The authors identified 13 RCTs, one prospective cohort study, four retrospective cohort studies, and one matched case control study. All but two were identified in other SRs. Only additonal data relating to Kuiper 2019 and St-Onge are data extracted here.

b. Defined as blood loss over 400 mL in the first hour after surgery or over 100 mL/hour for four consecutive hours; or drainage volume > 1000 mL within first 24 hours;

c. Defined as transfusion of more than 10 U of RBCs; or more than 20 U of any allogenic blood product

d. Units in 24 hours. Propensity-score matched cohort.

e. Favours intervention $p < 0.01$, I2 = 0%

STUDY DETAILS: Bugaev 2020			
Citation			
Bugaev N, Como J J, Golani G, Freeman J J, Sawhney J S, Vatsaas C J, Yorkgitis B K, Kreiner L A, Garcia N M, Abdel Aziz H, Pappas P A, Mahoney E J, Brown Z W, Kasotakis G. Thromboelastography and rotational thromboelastometry in bleeding patients with coagulopathy: Practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2020. 89:999-1017. DOI: 10.1097/TA.0000000000002944			
Affiliation/Source of funds			
Author affiliations: Tufts Medical Centre, Tufts University School of Medicine, Boston, Massachusetts; MetroHealth Medical Centre, Cleveland, Ohio; Soroka Medical Centre, Beer Sheva, Israel; TCU and UNTHSC School of Medicine, Fort Worth, Texas; Maine Medical Centre, Portland, Maine; Duke University School of Medicine, Durham, North Carolina; University of Florida College of Medicine—Jacksonville, Jacksonville, Florida; Case Western University School of Medicine, Cleveland, Ohio; Brody School of Medicine, East Carolina University, Greenville; Weill Cornell University, Doha, Qatar; College of Medicine, University of Central Florida, Orlando; Uniformed Services University of the Health Sciences, Bethesda; Conflicts of interest: The authors declare no conflicts of interest. *Funding:* Not reported.			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review and meta-analysis of 38 studies in total. In PICO 1, a total of 7 studies were selected including RCTs (2), retrospective studies (4) a prospective study (1).	I-III	Not reported	Trauma
Intervention		**Comparator**	
Schochl 2011: ROTEM Schaden 2012: ROTEM Nardi 2015: ROTEM Gonzalez 2016: ROTEM (RCT) Prat 2017: ROTEM Guth 2019: TEG Unruh 2019: ROTEM		Schochl 2011: No ROTEM Schaden 2012: No ROTEM Nardi 2015: No ROTEM Gonzalez 2016: No ROTEM (RCT) Prat 2017: No ROTEM Guth 2019: No TEG Unruh 2019: No ROTEM	

STUDY DETAILS: Bugaev 2020				
Population characteristics				
Schochl 2011: Severely injured patients with Injury Severity Score > 15 who required blood transfusions Guth 2019: Patients requiring any blood product transfusions Schaden 2012: Patients with burns Unruh 2019: Patients requiring MTP activation Gonzalez 2016: Patients requiring MTP activation Prat 2017: Severely injured patients with Injury Severity Score > 15 who required blood transfusions Nardi 2015: Severely injured patients with Injury Severity Score > 15 who required blood transfusions				
Length of follow-up			**Outcomes measured**	
Databases searched: PubMed, Embase, Cochrane Library, Web of Science and Ovid Medline (from inception to June 2019).			Mortality Blood product transfusions Need for additional haemostatic interventions	
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Moderate *Description:* More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It ***may*** provide an accurate summary of the results of the available studies that were included in the review. *Risk of bias of included studies:* The overall quality of evidence was determined to be very low.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD (n)**	**[comparator]** **n/N (%)** **Mean ± SD (n)**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
TEG/ROTEM vs no TEG/TOTEM				
Mortality N = 1488 (6 studies)	82/466 (17.6%)	158/1042 (15.2%)	RR 0.75 (0.59, 0.95)	*Favours TEG/ROTEM* *p* = 0.02 No significant heterogeneity I^2 = 0% (*p* = 0.60)
Prat 2017	4/85 (4.7%)	7/134 (5.2%)	RR 0.90 (0.27, 2.99)	
Schochl 2011	6/80 (7.5%)	60/601 (10%)	RR 0.75 (0.34, 1.68)	
Gonzalez 2016	11/56 (19.6%)	20/55 (36.4%)	RR 0.54 (0.29, 1.02)	
Nardi 2015	13/96 (13.5%)	26/130 (20%)	RR 0.68 (0.37, 1.25)	
Unruh 2019	15/47 (32.0%)	11/20 (55%)	RR 0.58 (0.33, 1.03)	
Guth 2019	33/102 (32.4%)	34/102 (33.3%)	RR 0.87 (0.66, 1.44)	
Number of RBCs transfused, Units N = 1459 (7 studies)	N = 480	N = 979	SMD –0.38 (–0.64, –0.12)	*Favours TEG/ROTEM* *p* = 0.004 Significant heterogeneity I^2 = 74% (*p* = 0.0008)
Schaden 2012	3.1±1.6 (14)	4.3±2.2 (16)	SMD –0.85 (–1.60, –0.10)	
Unruh 2019	6±5.2 (47)	11±3.7 (20)	SMD –1.03 (–1.58, –0.47)	
Gonzalez 2016	9.5±8.1 (56)	11±8.1 (55)	SMD –0.18 (–0.56, 0.19)	
Prat 2017	2±2.2 (85)	2±1.5 (55)	SMD 0.00 (–0.34, 0.34)	
Guth 2019	2±3 (102)	6±7.4 (102)	SMD –0.71 (–0.99, –0.42)	
Nardi 2015	6.5±4.8 (96)	8.1±6.7 (130)	SMD –0.27 (–0.53, –0.00)	
Schochl 2011	5.5±7 (80)	6±5.2 (601)	SMD –0.09 (–0.33, 0.14)	
Number of PLTs transfused, Units N = 404 (3 studies)	N = 199	N = 205	MD –0.44 (–1.05, 0.17)	No significant difference *p* = 0.16 Moderate heterogeneity I^2 = 55% (*p* = 0.11)
Nardi 2015	2.7±4.8 (96)	4.2±5.9 (130)	MD –1.50 (–2.90, –0.10)	
Gonzalez 2016	1±1.5 (56)	1±1.5 (55)	MD 0.00 (–0.56, 0.56)	
Unruh 2019	1.5±1.5 (47)	2±0.7 (20)	MD –0.50 (–1.03, 0.03)	

STUDY DETAILS: Bugaev 2020				
Number of FFP transfused, Units N = 827 (5 studies)	N = 386	N = 441	SMD –0.29 (–0.91, 0.34)	No significant difference p = 0.36 Significant heterogeneity I^2 = 94 (p < 0.00001)
Unruh 2019	4.5±4.1 (47)	4±4.1 (20)	SMD 0.12 (–0.40, 0.64)	
Gonzalez 2016	5±4.4 (56)	6±3.7 (55)	SMD –0.24 (–0.62, 0.13)	
Guth 2019	0.5±1.5 (102)	5±5.2 (102)	SMD –1.17 (–1.47, –0.87)	
Prat 2017	2±2.6 (85)	1±1.5 (134)	SMD 0.50 (0.22, 0.77)	
Nardi 2015	4.2±4.6 (96)	9±9.5 (130)	SMD –0.61 (–0.88, –0.34)	
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats. The studies included patients requiring MTP, patients with burns and severely injured patients. The studies cover a wide range of trauma patients.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats.				
Additional comments				
Authors conclusions: We conditionally recommend using TEG/ROTEM to guide blood transfusions instead of traditional coagulation parameters in each of the following three groups: adult trauma patients, adult surgical patients, and adult critically ill patients with ongoing haemorrhage and concern for coagulopathy. *List of relevant included studies:* Schaden 2012, Unruh 2019, Gonzalez 2016, Prat 2017, Guth 2019, Nardi 2015, Schochl 2011				

CI, confidence interval; FFP, fresh frozen plasma; MD, mean difference; MTP, massive transfusion protocol; PLT, platelets; pRBC, packed red blood cells; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; SMD, standard mean difference

a.Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I2 < 25%; (ii) mild heterogeneity if I2 < 25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 > 50%.

STUDY DETAILS: Amgalan 2020			
Citation			
Amgalan A, Allen T, Othman M, Ahmadzia H K. Systematic review of viscoelastic testing (TEG/ROTEM) in obstetrics and recommendations from the women's SSC of the ISTH. J Thromb Haemost. 2020; 18:1813-1838. DOI: 10.1111/jth.14882			
Affiliation/Source of funds			
Author affiliations: Georgetown University School of Medicine, Washington, DC, USA; Department of Anesthesiology, Duke University Hospital, Durham, NC, USA; Department of Biomedical and Molecular Sciences, School of Medicine, Queen's University, Kingston, ON, Canada; School of Baccalaureate Nursing, St. Lawrence College, Kingston, ON, Canada; Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA Conflicts of interest: The authors declared no conflicts of interest *Funding:* Not reported			
Study design	**Level of evidence**	**Location**	**Setting**
Systematic review of 93 studies (1 RCT)	I/II-IV	Not reported	Obstetrics
Intervention		**Comparator**	
ROTEM Collins 2017: Patients transfused with fibrinogen concentrate if FIBTEM ≤ 15 mm Mallaiah 2015: Fibrinogen phase (ROTEM-guided)		No ROTEM Collins 2017: Patients transfused with placebo if FIBTEM ≤ 15 mm Mallaiah 2015: 'Shock Pack' (4 units of RBCs, 4 units of FFP, & 1 adult dose of PLTs) used to correct coagulation deficits	
Population characteristics			
Collins 2017: Women aged ≥ 18 years and ≥ 24 weeks gestation with ongoing major PPH (1000-1500 mL blood loss) Snegovskikh 2017: women with severe PPH			

STUDY DETAILS: Amgalan 2020				
Mallaiah 2015: Women who had a MOH (estimated blood loss >1500mL) associated with coagulopathy (FIBTEM A5 < 12 mm, indicative of a plasma fibrinogen level of 2 g/l). McNamara 2019: Women with MOH				
Length of follow-up			**Outcomes measured**	
Databases searched: Ovid Medline (from 1989 to 2020)			Collins 2017: NR Snegovskikh 2017: ICU admissions Mallaiah 2015: TACO McNamara 2019: number of units; TACO	
INTERNAL VALIDITY				
Overall QUALITY of the systematic review (descriptive)				
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* The authors noted that a limitation of TEG/ROTEM studies is that several studies are undermined by poor Study design and/or risk of bias.				
RESULTS:				
Outcome **No. patients** **(No. trials)**	**[intervention]** **n/N (%)** **Mean ± SD**	**[comparator]** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity[a]** **I^2 (*p*-value)**
ROTEM versus no ROTEM				
Morbidity N = 20 349 (1 study) Snegovskikh 2017	Patients given treatment guided by ROTEM received significantly less frequent transfusions, underwent fewer hysterectomies, had fewer ICU admissions, and had shorter hospitalizations compared with those who were managed with the more traditional empiric protocol.			NR
Morbidity N = 663 (1 study) Collins 2017	Infusion of FC at FIBTEM A5 ≤ 15 mm did not improve outcomes in PPH. Findings suggest that fibrinogen replacement is not required if the FIBTEM A5 is > 12 mm or Clauss fibrinogen > 2 g/L, but an effect below these levels cannot be excluded.			No results
TACO N = 348 (2 studies) N = 255, McNamara 2019 N = 93, Mallaiah 2015	 NR 0%	 NR 9.5%	 NR NR	*Favours ROTEM* *p* < 0.002 *p* = 0.038
RBC transfused, Units N = 255 (1 study) McNamara 2019	 NR	 NR	 NR	 *Favours ROTEM* *p* < 0.0001
Transfusion requirements 1 study, N = 93 Mallaiah 2015 total blood components plasma CRYO massive transfusion (≥ 6 units) of RBCs	NR	NR	NR	*Favours ROTEM* *p* = 0.004 *p* < 0.0001 *p* < 0.0001 *p* = 0.0299
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is applicable to the Australian healthcare context.				

STUDY DETAILS: Amgalan 2020
Additional comments
Authors conclusions: The 93 studies included in this review demonstrate potential utility of TEG/ROTEM in obstetrics, but several of them had limitations in their Study design and/or their results were confounded by biases. The most robust evidence supporting the use of viscoelastic tests in obstetrics is for PPH, but its potential in managing hypercoagulable conditions is relatively under studied. Based on our review of the literature at this time, the routine use of ROTEM may best serve a role in clinically guiding transfusion therapy in obstetrics and identifying patients at risk for severe haemorrhage. Further studies, ideally large controlled multicentre clinical trials, are needed to broaden the applicability of TEG/ROTEM in obstetrics, validate TEG/ROTEM-guided approaches and design hospital protocols, and determine their effects on clinical outcomes to reduce morbidity and mortality in obstetrics. *List of relevant included studies:* Snegovskikh 2017, McNamara 2019, Mallaiah 2015, Collins 2017

CI, confidence interval; ICU, intensive care unit; MOH, massive obstetric haemorrhage; NR, not reported; PPH, post-partum haemorrhage; SD, standard deviation; TACO, Transfusion associated circulatory overload; TXA, tranexamic acid

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

Randomised controlled trials

STUDY DETAILS: Gonzalez 2016 (NCT01536496)			
Citation			
Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Annals of surgery. 2016;263(6):1051-9. NCT01536496: Study results are published here: https://clinicaltrials.gov/ct2/show/results/NCT01536496			
Affiliation/Source of funds			
No declarations of conflicts of interest available. The study was sponsored by: Denver Health and Hospital Authority in Collaboration with Haemonetics Corporation. Information provided by (Responsible Party): Ernest E. Moore, MD, Denver Health and Hospital Authority			
Study design	**Level of evidence**	**Location**	**Setting**
Randomised controlled trial	II	Denver, Colorado; USA	Single centre, trauma setting
Intervention		**Comparator**	
Blood product transfusion based on rapid thromboelastography (r-TEG) results. The current institutional massive transfusion protocol will be followed		Blood product transfusion based on conventional coagulation tests (aPTT, INR, fibrinogen level, D-dimer) to diagnose and describe post-injury coagulopathy and to guide blood product replacement. The current institutional massive transfusion protocol will be followed.	
Population characteristics			
Adults patients (aged >18 yrs) with blunt or penetrating trauma sustained < 6 hours before admission, with Injury Severity Score greater than 15, likely to require transfusion of RBC within 6 hours from admission as indicated by clinical assessment. The median age (IQR) was 30 (24 to 43), and 70.3% male. The number of patients with blunt vs penetrating trauma was not reported.			
Length of follow-up		**Outcomes measured**	
Lost to follow up and follow up details not reported. Mortality is reported at 28 days, in hospital. Timeframe of follow up for AEs is up to 28 days of hospitalisation		28 Day In-hospital Mortality Deaths Specified as Early Mortality (<6 Hours Post-injury) and Delayed Mortality (6-24 Hours Post-injury). Deaths Related to Coagulopathic Bleeding Based Upon Clinical Impressions of the Treating Surgeons and Review of Operative Records and Outcome (Hours Since Injury). Composition and Quantity of Blood Products Transfused at 24 Hours Post-injury	

STUDY DETAILS: Gonzalez 2016 (NCT01536496)				
		Number of Participants With Multiple Organ Failure (MOF) During This Hospitalization.		
INTERNAL VALIDITY				
Overall risk of bias (descriptive)				
Rating: High *Description:* The study has plausible bias that seriously weakens confidence in the results. Study is not published in a peer reviewed journal. Details regarding randomisation, allocation concealments and blinding of outcomes assessment not reported.				
RESULTS				
Population analysed	**Intervention**		**Comparator**	
Randomised	57		57	
Efficacy analysis (ITT)	56		55	
Efficacy analysis (PP)	56		55	
Safety analysis	56		55	
Outcome	**Intervention n/N (%) Mean ± SD**	**Comparator n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
TEG-r versus SoC				
Mortality (28 day)	11/56 (19.6)	20/55 (36.4)		*Favours Intervention* *p* = 0.049
Mortality (deaths < 6 hrs from injury)	4/56 (7.1)	11/55 (20)		Not reported
Mortality (deaths 6 to 24 hrs from injury)	7/56 (12.5)	8/55 (14.5)		Not reported
Deaths due to coagulopathic bleeding	5/56 (8.9)	11/55 (19.6)		Not reported
Deep vein thrombosis	8/56 (14.3)	6/55 (10.9)		*p* = 0.599
Pulmonary embolism	1/56 (1.8)	0/55 (0)		*p* = 1.01
MOF	2/56 (3.6)	3/55 (5.5)		Not reported
RBC transfusion volume, Units	Median (IQR) 9.5 (5, 16)	Median (IQR) 11.0 (6, 16)		Not reported
Plasma transfusion volume, units	Median (IQR) 5 (3 to 9)	Median (IQR) 0 (4 to 9)		Not reported
Cryoprecipitate transfusion volume, units	Median (IQR) 0 (0 to 2)	Median (IQR) 1.0 (0 to 2)		Not reported
Platelet transfusion volume, units	Median (IQR) 1 (0 to 2)	Median (IQR) 1 (0 to 2)		Not reported
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: The authors conclusions were not available.				

aPPT, activated partial thromboplastin time; CI, confidence interval; INR, international normalised ratio; ITT, intent to treat; MOF, multiple organ failure; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial

STUDY DETAILS: Baksaas-Aasen 2020			
Citation			
Baksaas-Aasen K, Gall L S, Stensballe J, Juffermans N P, Curry N, Maegele M, Brooks A, Rourke C, Gillespie S, Murphy J, Maroni R, Vulliamy P, Henriksen H H, Holst Pedersen K, Kolstadbraaten K M, Wirtz M R, Kleinveld J B, Schafer N, Chinna S, Davenport R A, Naess P A, Goslings J C, Eaglestone S, Stanworth S, Johansson P I, Gaarder C and Brohi K. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. Intensive Care Med. 2021. 47:49-59. https://doi.org/10.1007/s00134-020-06266-1			
Affiliation/Source of funds			
Author affiliations: Oslo University Hospital & University of Oslo, Oslo, Norway; Centre for Trauma Sciences, Queen Mary University of London, Blizard Institute, 4 Newark Street, London E1 2AT, UK; Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Amsterdam University Medical Centres, Amsterdam, The Netherlands; Oxford University Hospital NHS Trust, Oxford, UK; Cologne-Merheim Medical Centre, University of Witten/Herdecke, Cologne, Germany; Nottingham University Hospitals NHS Trust, Nottingham, UK; Queen Mary University of London, London, UK; NHS Blood and Transplant, Bristol, UK. Conflicts of interest: Astra Zeneca, Bayer, CSL Behring, IL-Werfen/TEM International, LFB Biomedicaments, Portola Inc., Haemonetics Corp., TEM International, Johnson and Johnson, Octapharma AG., Nycomed. And Bayer. *Funding:* The study was funded by the European Commission. Both TEM® International GmbH and Haemonetics® Corporation were collaborating organizations in the program.			
Study design	**Level of evidence**	**Location**	**Setting**
Randomised controlled trial	II	Denmark The Netherlands Norway Germany UK	Multicentre, trauma
Intervention		**Comparator**	
Viscoelastic Haemostatic Assays (VHA) All patients received their local hospital's standard MHP, based on the empiric delivery of tranexamic acid, blood components delivered in a 1:1:1 ratio of RBCs, plasma and platelet transfusions and limited infusion of crystalloid fluids.		*Conventional Coagulation Tests (CCT)* All patients received their local hospital's standard MHP, based on the empiric delivery of tranexamic acid, blood components delivered in a 1:1:1 ratio of RBCs, plasma and platelet transfusions and limited infusion of crystalloid fluids.	
Population characteristics			
Adult trauma patients with clinical signs of bleeding activating the local MHP and if RBC transfusion had been initiated, randomised within 3 hours of injury and maximum of 1 hour after admission into the emergency department.			
Length of follow-up		**Outcomes measured**	
Drop-out rate: 15/411 patients (3.6%) Missing data: Participants with missing data for a measure were excluded from any statistical comparisons regarding that measure.		Mortality (at 6 hrs, 24 hrs, 28 days, 90 days) Total blood components Symptomatic thromboembolic events Multiple organ dysfunction Serious adverse events (infection, thromboembolic, ischemic, organ failure, acute kidney injury, acute lung injury, new onset major bleeding, cardiac, neurological, other)	
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: High *Description:* The study has plausible bias that seriously weakens confidence in the results.			

STUDY DETAILS: Baksaas-Aasen 2020				
RESULTS				
Population analysed	**Intervention**		**Comparator**	
Randomised	201		195	
Efficacy analysis (ITT)	201		195	
Efficacy analysis (PP)	150		163	
Safety analysis	201		195	
Outcome	**Intervention n/N (%) Mean ± SD**	**Comparator n/N (%) Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
VHA versus CCT				
Mortality, 6 hrs N = 396	22/201 (11%)	22/195 (11%)	OR 0.97 (0.52,1.80)	No significant difference *p* = 0.915
Mortality, 24 hrs N = 396	29/201 (14%)	33/195 (17%)	OR 0.83 (0.48, 1.42)	No significant difference *p* = 0.495
Mortality, 28 days N = 395	50/201 (25%)	55/194 (28%)	OR 0.84 (0.54, 1.31)	No significant difference *p* = 0.435
Mortality, 90 days N = 356	53/179 (29%)	56/177 (31%)	OR 0.91 (0.58, 1.42)	No significant difference *p* = 0.678
Death from exsanguination N = 107	13/51 (25%)	17/56 (30%)	OR 0.78 (0.34, 1.82)	No significant difference *p* = 0.576
Morbidity, MOD N = 323	141/164 (86%)	124/159 (84%)	OR 1.14 (0.62, 2.10)	No significant difference *p* = 0.668
Thromboembolic events (SAE) N = 396	15/201 (7.5%)	22/195 (11.3%)	NR	NR
Symptomatic thromboembolic events N = 396	17/201 (9%)	27/195 (14%)	OR 0.57 (0.31, 1.08)	No significant difference *p* = 0.088
Infection (SAE) N = 396	29/201 (14.4%)	30/195 (15.4%)	NR	NR
Ischemic (SAE) N = 396	6/201 (3.0%)	0/195	NR	NR
Organ failure (SAE) N = 396	9/201 (4.5%)	5/195 (2.6%)	NR	NR
Acute kidney injury (SAE) N = 396	6/201 (3.0%)	6/195 (3.1%)	NR	NR
Acute lung injury (SAE) N = 396	8/201 (4.0%)	5/195 (2.6%)	NR	NR
New onset major bleeding (SAE) N = 396	6/201 (3.0%)	9/195 (4.6%)	NR	NR
Cardiac (SAE) N = 396	10/201 (5.0%)	6/195 (3.1%)	NR	NR
Neurological (SAE) N = 396	4/201 (2.0%)	0/195	NR	NR
Other (SAE) N = 396	8/201 (4.0%)	10/195 (5.1%)	NR	NR

STUDY DETAILS: Baksaas-Aasen 2020				
Massive transfusion at 24 hours N = 396	53/201 (26%)	55/195 (28%)	OR 0.91 (0.59, 1.42)	No significant difference *p* = 0.682
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population. The RCT was conducted in large hospitals with 396 patients.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context. The studies were conducted in countries with similar healthcare systems to Australia.				
Additional comments				
Authors conclusions: When standard care is delivered to bleeding trauma patients, with empiric balanced transfusion therapy and intensive CCT monitoring, VHAs identify more coagulation deficits and deliver additional haemostatic interventions. However, all patients do not benefit from this approach and further research is required to identify injury types and physiologies that may benefit from this approach. Additional analyses should also explore the coagulation deficits identified by VHA alone, and the response of the coagulation system to the algorithm-prescribed haemostatic agents.				

CCT, conventional coagulation tests; CI, confidence interval; IQR, interquartile range; MHP, massive haemorrhage protocol; NR, not reported; OR, odds ratio; RBC, red blood cells; RCT, randomised controlled trial; SAE, serious adverse event; SD, standard deviation; VHA, viscoelastic haemostatic assays

Observational / cohort studies

STUDY DETAILS: Wang 2017			
Citation			
Wang, H., Robinson, R. D., Phillips, J. L., Ryon, A., Simpson, S., Ford, J. R., Umejiego, J., Duane, T. M., Putty, B., & Zenarosa, N. R. (2017). Traumatic Abdominal Solid Organ Injury Patients Might Benefit From Thromboelastography-Guided Blood Component Therapy. J Clin Med Res, 9(5), 433-438. doi:10.14740/jocmr3005w			
Affiliation/Source of funds			
The authors declared no conflicts of interest, and no funding was received.			
Study design	**Level of evidence**	**Location**	**Setting**
Retrospective cohort	III-2	Texas, USA	Single centre, Trauma
Intervention		**Comparator**	
TEG guided blood component therapy		Standard of care (TEG-guided BCT not strictly managed)	
Population characteristics			
Patients sustaining traumatic liver and/or spleen injuries were enrolled. 71% Caucasian, 22% African American 81% Blunt injury Patients in non-TEG group tended to be older, lower initial systolic blood pressure, and more severe injury severity.			
Length of follow-up		**Outcomes measured**	
June 2012-December 2015		Blood component transfusions (PRBCs, FFP, PLTs, CRYO) Length of stay In hospital mortality (< 24 hr, > 24 hr)	
Method of analysis			
Pearson's Chi-square ($\chi 2$) analysis was used to analyse differences in relative frequencies among groups for categorical variables. Student's t-tests and Wilcoxon rank-sum (Mann-Whitney) test were used to test differences between groups for continuous variables.			
INTERNAL VALIDITY			
Overall risk of bias (descriptive)			
Rating: Serious *Description:* The study is too problematic and does not provide any useful evidence with regards to mortality and blood transfusion requirements. Concerns regarding selection bias and inability to control confounding. This study has a small sample size (N<100 in each group).			
RESULTS			

Population analysed	**Intervention**		**Comparator**	
Available	86		80	
Analysed	86		80	
Outcome	**Intervention** **n/N (%)** **Mean ± SD (n)**	**Comparator** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value**
TEG vs Soc				
Mortality, in hospital (total) N = 166	12/86 (14)	19/80 (15)	NR	No significant difference NR
RBC transfused, Units N = 166	4 ± 7 (86)	9 ±10 (80)	NR	*Favours intervention* $p < 0.01$
FFP transfused, Units N = 166	1 ± 5 (86)	5 ± 6 (80)	NR	*Favours intervention* $p < 0.01$
PLTs transfused, Units N = 166	0.4 ± 1.5 (86)	2.9 ± 4.8 (80)	NR	*Favours intervention* $p < 0.01$
CRYO transfused, Units	0.1 ± 0.5 (86)	0.3 ± 1.2 (80)	NR	No significant difference

N = 166				NR
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats				
Additional comments				
Authors conclusions: Traumatic abdominal solid organ (liver and/or spleen) injury patients receiving blood transfusion might benefit from TEG-guided blood component transfusions indicated by less blood products used and associated with shortened hospital stay amongst the cohort. The authors acknowledged the limitations of the study due to small sample size, limited information accuracy, missing data and potential selection bias.				

CI, confidence interval; CRYO, cryoprecipitate; FFP, fresh frozen plasma; ITT, intention-to-treat; NR, not reported; PRBC, packed red blood cells; RCT, randomised controlled trial; SD, standard deviation

E9 Cell salvage (Question 9)

Systematic reviews/meta-analyses

<table>
<tr><td colspan="4">STUDY DETAILS: Shantikumar 2011</td></tr>
<tr><td colspan="4">Citation</td></tr>
<tr><td colspan="4">Shantikumar, S., Patel, S., & Handa, A. (2011). The role of cell salvage autotransfusion in abdominal aortic aneurysm surgery. European Journal of Vascular & Endovascular Surgery, 42(5), 577-584. doi:https://dx.doi.org/10.1016/j.ejvs.2011.04.014</td></tr>
<tr><td colspan="4">Affiliation/Source of funds</td></tr>
<tr><td colspan="4">UK John Radcliffe Hospital, Oxford; Wycombe Hospital, High Wycombe
The authors declared they had no conflicts of interest or funding source.</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location*</td><td>Setting</td></tr>
<tr><td>SR of available evidence of any study type</td><td>Level I / III</td><td>Markovic 2009: Serbia
Posacioglu 2002: Turkey
Shuhaiber 2003: UK
Tawfick 2008: Germany
Serracino-Inglott 2005: UK

* Details retrieved from primary studies</td><td>Vascular surgery
Markovic 2009: SC
Posacioglu 2002: SC
Shuhaiber 2003: SC
Tawfick 2008: SC
Serracino-Inglott 2005: regional database</td></tr>
<tr><td colspan="2">Intervention</td><td colspan="2">Comparator</td></tr>
<tr><td colspan="2">Five non-randomised controlled studies reported the role of cell salvage in ruptured aneurysm repairs. Only these studies are included here as per the PICO criteria for question 9 (see comments below).
Cell salvage
No explicit restriction on any parameters.
Individual studies had different transfusion thresholds:
Markovic 2009: Hb < 10g/dL
Posacioglu 2002: Hct < 28%
Shuhaiber 2003: Hb < 10g/dL
Tawfick 2008: Hb < 8.5g/dL
Serracino-Inglott 2005: not defined
Due to the differences in transfusion thresholds across studies, the results could not be pooled.</td><td colspan="2">No cell salvage/any</td></tr>
<tr><td colspan="4">Population characteristics</td></tr>
<tr><td colspan="4">Patients undergoing abdominal-aortic aneurysm (AAA) repair, excluding procedures for aorto-occlusive disease (AOD).
Characteristic of patients in included studies not reported.
Noted there was no mention as to the location of the aneurysms in Tawfick 2008.</td></tr>
<tr><td colspan="2">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="2">Databases searched: PubMed, Embase, Cochrane
Search date: from database inception to August 2010
Limited to English language</td><td colspan="2">Transfusion threshold, blood-product use, proportion of patients transfused, complications, ICU stay, and hospital stay.</td></tr>
<tr><td colspan="4">INTERNAL VALIDITY</td></tr>
<tr><td colspan="4">Overall QUALITY of the systematic review (descriptive)</td></tr>
<tr><td colspan="4">Rating (AMSTAR): Critically low
Description: More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.
Risk of bias of included studies: The study authors did not assess risk of bias of the included studies and did not consider this in their analysis. Justifications for exclusion of articles was not provided.</td></tr>
</table>

STUDY DETAILS: Shantikumar 2011				
RESULTS:				
Outcome **No. patients (No. trials)**	**Cell salvage** **n/N (%)** **Mean ± SD (n)**	**No cell salvage** **n/N (%)** **Mean ± SD (n)**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
Mortality				
Posacioglu 2002	NR	NR	NR	NR No significant difference
Serracino-Inglott 2005	NR/40 (76)	NR/114 (56)	NR	NR *Favours cell salvage* [e]
Post-operative complications				
Serracino-Inglott 2005	NR	NR	NR	NR No significant difference
Mean red cell transfusion (units)	Est. 3.6	Est. 7.0	NR	
Markovic 2009	0.5 ± NR (30)	2.2 ± NR (30)	NR	*p* = 0.009 *Favours cell salvage*
Posacioglu 2002	3.6 ± NR (40)	5.8 ± NR (16)	NR	*p* = 0.026 *Favours cell salvage* [b]
Serracino-Inglott 2005	4 ± NR (40)	7 ± NR (114)	NR	*p* < 0.001 *Favours cell salvage* [c]
Shuhaiber 2003	8 ± NR (4)	9 ± NR (21)	NR	NR No significant difference
Tawfick 2008	6 ± NR (27)	12 ± NR (28)	NR	*p* < 0.001 *Favours cell salvage* [d]
Mean FFP (units)				
Posacioglu 2002	1.5 ± NR (40)	4.5 ± NR (16)	NR	*p* = 0.006 [b]
Tawfick 2008	NR (27)	NR (28)	NR	NR No significant difference
Mean PLT (units)				
Tawfick 2008	NR (27)	NR (28)	NR	NR No significant difference
Length of hospital stay				
Posacioglu 2002	NR	NR	NR	NR Shorter in the CS group
Tawfick 2008	NR	NR	NR	NR Shorter in the CS group
Additional data from primary studies retrieved				
Mortality, any timepoint up to 30 days				
Markovic 2009	12/30 (40)	14/30 (46.6)	NR	*p* = 0.062 No difference [f]
Posacioglu 2002	16/40 (40)	8/16 (50)	NR	*p* = 0.495 No difference [f]
Tawfick 2008	6/27 (22)	9/28 (32)	NR	NR
Serracino-Inglott 2005	NR/40 (68)	NR/114 (51)	NR	*p* = 0.07 No difference
Serracino-Inglott 2005 [e]	NR (79)	NR (56)	NR	*p* = 0.01 *Favours cell salvage*
Mortality, 30 days Shuhaiber 2003	Given there were only four patients in the intervention group, no meaningful difference in mortality between groups could be observed. Overall, 10/25 (40%) patients in the study cohort died.			
Mortality, intraoperative Markovic 2009	7/30	4/30	NR	
Mortality, postoperative Markovic 2009	5/30 (16.67)	10/30	NR	
Postoperative complications Marcovic 2009	Data were presented for entire study cohort that includes elective AAA and AOD. The authors noted no significant difference between study groups for transfusion-related complications, multi-organ failure; stroke, myocardial infarction, wound infection, bleeding, colon ischemia, respiratory failure, renal failure, or reoperation.			
Postoperative complications Shuhaiber 2003	Given there were only four patients in the intervention group, no meaningful difference in complications could be observed. Overall, 14/25 (56%) patients had major complications including haemorrhage and anastomotic leak, infection, non-graft thrombosis, embolism, myocardial infarction, arrythmia, cardiac failure, impaired renal function, and respiratory failure.			

STUDY DETAILS: Shantikumar 2011				
Postoperative complications Tawfick 2008	Data were presented for entire study cohort that includes elective and emergency AAA. The authors noted no significant difference between study groups for respiratory complications (ARDS, pneumonia, atelectasis) or cardiac complications (arrythmias, ischemic cardiac event). A significant effect favouring no cell salvage observed for need to renal dialysis (p = 0.037).			
Postoperative respiratory complications Posacioglu 2002	16/40 (40)	2/16 (12.5)	NR	p = 0.047 *Favours no cell salvage*
Postoperative renal complications Posacioglu 2002	10/40 (25)	2/16 (12.5)	NR	p = 0.475 No difference
Postoperative GI complications Posacioglu 2002	4/40 (10)	1/16 (6.25)	NR	p = 1.00 No difference
Re-operation Posacioglu 2002	6/40 (15)	2/16 (12.5)	NR	p = 0.588 No difference
Intraoperative RBC transfusion volume, mL Markovic 2009	913.8 ± 602 (30)	1146.3 ± 595 (30)	NR	p = 0.038 *Favours cell salvage*
Postoperative RBC transfusion volume, mL Markovic 2009	976.3 ± 927 (30)	1609.6 ± 998 (30)	NR	p = 0.0097 *Favours cell salvage*
Total allogenic RBC transfusion volume, mL Markovic 2009 Shuhaiber 2003	1890.1 ± 1186 (30) 2800 ± 857 (4)	2755.9 ± 1265 (30) 3161 ± 2155 (21)	NR NR	p = 0.0089 *Favours cell salvage* p = NR No significant difference
Total RBC transfusion volume, units Posacioglu 2002 Tawfick 2008 Serracino-Inglott 2005	5.8 ± 3.84 (40) 6 (range 0–34) (27) 4 (range 0–24) (40)	3.63 ± 2.87 (16) 12 (range 3–38) (28) 7 (range 0–29) (114)	NR NR NR	p = 0.026 *Favours no cell salvage* p = NR p < 0.01 *Favours cell salvage*
Intraoperative plasma transfusion volume, mL Markovic 2009	627.8 ± 508 (30)	817.0 ± 551 (30)	NR	p = 0.024 *Favours cell salvage*
Postoperative plasma transfusion volume, mL Markovic 2009	595.6 ± 1021 (30)	828.8 ± 640 (30)	NR	p = 0.041 *Favours cell salvage*
Total allogenic plasma transfusion volume, mL Markovic 2009	1223.4 ± 1223 (30)	1645.8 ± 947 (30)	NR	p = 0.062 No difference
Total FFP volume, units Posacioglu 2002	4.45 ± 4.03 (40)	1.5 ± 1.37 (16)	NR	p = 0.006 *Favours no cell salvage*
Length of hospital stay, days Posacioglu 2002 Shuhaiber 2003 Tawfick 2008	9.35 ± 7.566 (40) 13.8 ± 8.5 (4) 27.23 ± SE 1.021 (27) (range 2–138)	5.687 ± 4.301 (16) 12.6 ± 3.2 (21) 33.79 ± SE 0.435 (28) (range 3–122)	NR NR NR	p = 0.027 *Favours no cell salvage* p = NR No difference p = NR
Length of ICU stay, days Shuhaibezr 2003 Tawfick 2008	2.5 ± 1.7 (4)	7.9 ± 7.9 (21)	NR NR	p = NR p = NR

STUDY DETAILS: Shantikumar 2011				
	7.42 ± SE 1.043 (27) (range 2–30)	9.38 ± SE 1.647 (28) (range 2–45)		
Length of HDU stay, days Shuhaiber 2003	5 ± 2.7 (4)	5.9 ± 8.7 (21)	NR	*p* = NR
Length of ward stay, days Shuhaiber 2003	10 ± 7.9 (4)	12.8 ± 13.7 (21)	NR	*p* = NR
Costs	None of the included studies reported costs associated with cell salvage or allogenic transfusions specific to the emergency AAA patient population.			
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Guidelines population but could be sensibly applied. OR difficult to judge? Studies are in patients with ruptured abdominal aortic aneurysm repair, which is a narrower population than the guidelines (critical bleeding)				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is probably applicable to the Australian healthcare context with some caveats. Transfusion threshold varies across Australian hospitals and hence it is difficult to comment on the applicability of these results.				
Additional comments				
Authors conclusions: While some data are conflicting, cell salvage appears to reduce blood-product use in both elective and ruptured AAA repairs. Owing to heterogeneity in methodology (e.g. type of aneurysm [infrarenal/suprarenal/complex], the use of different transfusion devices, heparin administration/reversal, transfusion thresholds), further studies are required before cell salvage becomes standard practice. Whilst this suggests a role for routine cell salvage in aneurysm repairs, local protocols need to be based on the availability of cell salvage, the cost of blood products, the threshold for transfusion and the mean blood loss within the vascular unit. *List of relevant included studies:* Markovic 2009, Posacioglu 2002, Serracino-Inglott 2005, Shuhaiber 2003, Tawfick 2008 *List of excluded studies (not relevant):* The authors mention five uncontrolled studies and eight nonrandomised controlled studies in the elective setting that did not meet our PICO criteria.				

AAA, abdominal aortic aneurysm; AOD, aortoiliac occlusive disease; CI, confidence interval; Gi, gastrointestinal; MD, mean difference; RCT, randomised controlled trial; RR, relative risk; SC, single centre; SD, standard deviation

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Data for Posacioglu 2002 incorrectly reported (intervention and control groups swapped). The primary study reports an effect favouring no cell salvage.

c. Incorrectly reported by Shantikumar 2011. Reported as $p < 0.01$ in Serracino-Inglott 2005.

d. This *p*-value refers to the difference in mean units RBC transfused for both the elective and emergency patients (reported by Tawfick 2008).

e. Excludes patients who died in the theatre from the analysis (Serracino-Inglott 2005).

f. Study not sufficiently powered to detect a significant difference for this outcome.

STUDY DETAILS: Meybohm 2016
Citation
Meybohm, P., Choorapoikayil, S., Wessels, A., Herrmann, E., Zacharowski, K., & Spahn, D. R. (2016). Washed cell salvage in surgical patients: A review and meta-analysis of prospective randomized trials under PRISMA. ***Medicine***, 95(31), e4490. doi:https://dx.doi.org/10.1097/MD.0000000000004490 PROSPERO registration number: CRD42016035726
Affiliation/Source of funds
University Hospital Frankfurt, University Hospital Zurich, Goethe University Frankfurt, Germany The authors noted no pharmaceutical company funding of the study.

STUDY DETAILS: Meybohm 2016			
PM and KZ noted receiving honoraria with numerous companies associated with the conduct of a large clinical trial in the field of Patient Blood Management.			
Study design	**Level of evidence**	**Location**	**Setting**
SR of Level II studies	Level I	Bowley 2006: South Africa	SR: any surgical discipline Bowley 2006: trauma
Intervention		**Comparator**	
Intra- and/or postoperatively washed cell salvage (Cell saver)		No cell salvage	
Population characteristics			
Surgical patients with no limit of age nor type of surgery. Included urgent and non-urgent surgery. The authors identified 47 studies, 15 in orthopaedic surgery, 21 in cardiac surgery, 6 in vascular surgery, 1 in multiple trauma surgery, 2 in cancer surgery, and 2 in paediatric surgery. Of these, 1 study was considered relevant to the PICO criteria outlined for Question 9. - Bowley 2006: trauma surgery/massive bleeding Bowley 2006 randomised patients (aged > 18 years) presenting to emergency with penetrating torso injury requiring laparotomy and had exhibited hypotension (< 90 mm Hg); 91% (40/44) were male.			
Length of follow-up		**Outcomes measured**	
Databases searched: Medline, Cochrane library, grey literature Search dates: Not stated. Study published Jul 2016		Primary: number of patients exposed to allogeneic RBC transfusion Secondary: Number of units of allogeneic blood transfused, Number of patients exposed to re-operation for bleeding, Number of exposed patients to plasma, Number of exposed patients to platelets, infectious complications, myocardial infarction, stroke, mortality, Length of hospital stay	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): High *Description:* The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. *Risk of bias of included studies:* Bowley 2006: low risk of bias for patient selection, all other domains assessed as unclear or high, likely due to poor reporting (outcome assessment was not blinded)			
RESULTS:			
Outcome **No. patients (No. trials)**	**Cell salvage** **n/N (%)** **Mean ± SD**	**No cell salvage** **n/N (%)** **Mean ± SD**	**Risk estimate** **(95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity [a]** **I^2 (*p*-value)**
Trauma setting				
Patients exposed to allogeneic RBC transfusion N = 44 (1 trial) Bowley 2006	21/21 (100)	23/23 (100)	RR 1.00 (0.92, 1.09)	No significant difference *p* = 1.00
Number of units of allogeneic blood transfused, first 24 hours N = 44 (1 trial) Bowley 2006	6.47 ± 5.14 (21)	11.17 ± 6.06 (23)	MD –4.70 (–8.01, –1.39)	*Favours cell salvage* *p* = 0.005
Volume of FFP transfused, first 24 hours, units [b] N = 44 (1 trial)	4.76 ± 4.8 (21)	4.04 ± 4.3 (23)	MD 0.72 (–1.98, 3.42) [c]	No significant difference *p* = 0.6

STUDY DETAILS: Meybohm 2016				
Bowley 2006				
Volume of PLTs transfused, units [b] N = 44 (1 trial) Bowley 2006	1.0 ± 2.2 (21)	0.56 ± 0.94 (23)	MD 0.44 (–0.58, 1.46) [c]	No significant difference *p* = 0.40
Infections (sepsis) N = 44 (1 trial) Bowley 2006	5/21 (23.8)	7/23 (30.4)	RR 0.78 (0.29, 2.09)	No significant difference *p* = 0.62
Mortality, timing not specified [d] N = 44 (1 trial) Bowley 2006	14/21 (66.7)	15/23 (65.2)	RR 1.02 (0.67, 1.56)	No significant difference *p* = 0.92
Length of hospital stay (survivors), days [b] N = 44 (1 trial) Bowley 2006	15.7 ± 9.17 (7) (median 13)	14.6 ± 6.8 (8) (median 13)	MD 1.10 (–7.17, 9.37)	No significant difference *p* = 0.79
Financial cost, £ [b] N = 44 (1 trial) Bowley 2006	812.23 ± 451.23 (range 169.92, 1747.5)	990.4 ± 479.48 (range 19.9, 1753.3)	NR	No significant difference *p* = 0.2
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is directly generalisable to the Australian population with some caveats One study comparing cell salvage versus no cell salvage in patients undergoing multiple trauma surgery.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is directly applicable to the Australian healthcare context with few caveats The included study can be considered generally applicable the Australian health care system.				
Additional comments				
Out of the 47 trials included, only one trial (N = 44) included patients with trauma/massive transfusion. An additional seven studies were considered, but later deemed more appropriate for assessment in the perioperative module as patients were scheduled for elective surgery. *Authors conclusions* Washed cell salvage is efficacious in reducing the need to allogenic RBC transfusion and risk of infection in surgery.				

AAA, Abdominal aortic aneurysm; CI, confidence interval; FFP, fresh frozen plasma; MD, mean difference; mL, millilitre; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation; UK, United Kingdom; WMD, weighted mean difference

a. Only applicable to Level I studies with formal meta-analysis. 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 $I^2 > 50\%$.

b. Data sourced from primary study (Bowley 2006).

c. Calculated post-hoc using RevMan 5.3. I-V Random effects.

d. Cause of death was exsanguination (10/15) and MOF related to sepsis (5/15) in the control group; and exsanguination (8/14) or MOF related to sepsis (6/14) in the control group.

e. Transfusion data expressed in mLs were converted to units by dividing by 300.

f. Up to 24 hours, hospital stay, 3 years, or not specified.

STUDY DETAILS: Nayar 2017
Citation
Nayar, S. K., & Shafiq, B. (2017). Blood Conservation in Orthopaedic Trauma. *Techniques in Orthopaedics,* 32(1), 45-50. doi:http://dx.doi.org/10.1097/BTO.0000000000000208
Affiliation/Source of funds
The Johns Hopkins University School of Medicine

STUDY DETAILS: Nayar 2017			
Study design	**Level of evidence**	**Location**	**Setting**
Narrative review of Level II/III studies	Level I	Various	Orthopaedic trauma surgery
Intervention		**Comparator**	
Blood conservation methods in orthopaedic trauma surgery including: - Transfusion methods (autotransfusion, cell salvage, transfusion thresholds) - Pharmacological agents (tranexamic acid, erythropoietin and iron supplementation, fibrin and thrombin sealants - Operative techniques (hypotensive anaesthesia, normovolemic hemodilution, surgical approach)		Any	
Population characteristics			
The population varied across studies in terms of type of orthopaedic trauma surgery. Studies that focused on cell salvage during orthopaedic trauma surgery were reviewed for inclusion but later excluded as participants were not critically bleeding.			
Length of follow-up		**Outcomes measured**	
Databases searched: PubMed, Embase, Cochrane Library, Scopus, Global Health and WHO Global Health Library; Regional libraries Search dates: Not specified. Review published 2017		Cost Rate of blood transfusion	
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating (AMSTAR): Critically low *Description:* More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. *Risk of bias of included studies:* Risk of bias of included studies was not assessed.			
RESULTS:			

Outcome **No. patients (No. trials)**	**Cell salvage** **n/N (%)** **Mean ± SD**	**No cell salvage** **n/N (%)** **Mean ± SD**	**Risk estimate (95% CI)**	***Statistical significance*** ***p*-value** **Heterogeneity** **I^2 (*p*-value)**

EXTERNAL VALIDITY
Generalisability (relevance of the study population to the Guidelines target population)
Not assessed
Applicability (relevance of the evidence to the Australian health care system)
Not assessed
Additional comments
Nayar 2017 was a narrative review that assessed blood conservation strategies in the setting of acute orthopaedic trauma. The review authors identified seven nonrandomised studies in their discussion of cell salvage, however, did not provided any usable data. The primary studies were retrieved for further assessment. *Excluded studies* The studies were reviewed, but later deemed more appropriate for assessment in the perioperative module as patients were not critically bleeding. Bigsby 2013, Canan 2013, Cavallieru 1994, Firoozobadi 2015, Odak 2013, Scannell 2009, Schmidt 1998

AAA, Abdominal aortic aneurysm; CI, confidence interval; ITT, intention-to-treat; MD, mean difference; NR, not reported; PP, per-protocol; QALY, quality adjusted life year; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation

Randomised controlled trials

No additional studies identified.

Observational / cohort studies

STUDY DETAILS: Bhangu 2012			
Citation			
Bhangu, A., Nepogodiev, D., Doughty, H., Bowley D. (2012). Intraoperative cell salvage in a combat support hospital: a prospective proof of concept study. Transfusion, 1-6. doi: 10.1111/j.1537-2995.2012.03835.x			
Affiliation/Source of funds			
From the Joint Force Hospital, Camp Bastion, Afghanistan, Op HERRICK, BFPO 792. Details on funding not provided. The authors declared no conflicts of interest.			
Study design	**Level of evidence**	**Location**	**Setting**
Prospective cohort proof of concept study	III-2	Camp Bastion, Afghanistan	Trauma setting, combat support hospital
Intervention		**Comparator**	
Cell salvage via washed system using centrifuge		No cell salvage	
Population characteristics			
A total of 130 patients were admitted having sustained combat-related injury (76% blast-injury, 22% gun-shot, 2% road). Twenty-nine patients were judged by the attending military surgeon (DB) to be likely to require massive blood transfusion*, of which 27 were identified on admission. Eighteen cases were selected for intraoperative blood salvage and salvage was successfully completed in 17 (one patient died on operating table before cell salvage could occur). Eleven patients who underwent MT did not undergo cell salvage; nine patients arrived at the same time as other patients in whom cell salvage was planned or ongoing. The remaining two patients were not identified on admission but went on to require high volumes of blood products. *require at least 10 units of RBCs in the first 12 hours after injury (12 hr was taken as a cut-off, as International Security and Assistance Force casualties are evacuated to home nation as soon as possible, once clinical stability has been achieved).			
Length of follow-up		**Outcomes measured**	
No follow-up specified.		Volume of cell salvage required (units).	
Method of analysis			
Continuous data are presented as median and interquartile range (IQR); differences between groups were tested using the Mann-Whitney U test.			
INTERNAL VALIDITY			
Overall QUALITY of the systematic review (descriptive)			
Rating: Serious *Description:* The study has some important problems and does not to provide any useful evidence on the effectiveness of the intervention. There is insufficient information regarding patient characteristics to assess potential confounders.			

STUDY DETAILS: Bhangu 2012				
RESULTS				
Population analysed	**Cell salvage**		**No cell salvage**	
Available	17		11	
Analysed	17		11	
Outcome	**Cell salvage Median (IQR)**	**No cell salvage Median (IQR)**	**Risk estimate (95% CI)**	***Statistical significance p*-value**
Cell salvage vs no cell salvage				
Volume of RBC transfused, units N = 17 Mechanism of injury (n) GSW (4) Blast (13) Body area (n) Cavity (8) Extremity (9)	14 (9.5–18.5); range 2–27 11 (4.25–14.75) 17 (9.5–20.5) 9.5 (4.25–11.0) 18 (15.5–22.5)	Total 463 (n = 130)	The authors estimated a potential 7.6% reduction when compared to allogeneic transfusions in the overall 130 patient cohort; and a potential median reduction of 9..8% per patient.	NR Test for subgroup difference *p* = 0.212 *p* = 0.001
Volume of plasma transfused, units Mechanism of injury (n) GSW (4) Blast (13) Body area (n) Cavity (8) Extremity (9)	 11.5 (4.25–16.5) 17 (10–22) 10 (4–13.5) 21 (15.5–24)			 Test for subgroup difference *p* = 0.192 *p* = 0.004
Volume of PLTs transfused, units Mechanism of injury (n) GSW (4) Blast (13) Body area (n) Cavity (8) Extremity (9)	 2 (0.5–4.25) 3 (2–5) 2 (0.25–4.25) 3 (2.5–5.5)			 Test for subgroup difference *p* = 0.327 *p* = 0.050
Volume of CRYO transfused, units Mechanism of injury (n) GSW (4) Blast (13) Body area (n) Cavity (8) Extremity (9)	 1 (0.25–1.75) 2 (1–2) 1 (0–1.75) 2 (1–2)			 Test for subgroup difference *p* = 0.335 *p* = 0.046
EXTERNAL VALIDITY				
Generalisability (relevance of the study population to the Guidelines target population)				
The evidence is not directly generalisable to the Australian population but could be sensibly applied. Patients were admitted to a combat support hospital with battle-related injury. Blast injuries, often from improvised explosive devices, drive environmental material deep into patients' wounds, leading to gross contamination.				
Applicability (relevance of the evidence to the Australian health care system)				
The evidence is not applicable to the Australian healthcare context, and it is difficult to judge if it is sensible to apply.				

STUDY DETAILS: Bhangu 2012
Additional comments
The results of this study present more arguments against IBS than for it in a combat setting; showing that there is no place for IBS in the management of blast injury to the extremities. Nevertheless, IBS does have the potential to offer resilience during periods of limited RBC supply and further experimental, clinical, and economic evaluation is required.

CI, confidence interval; GSW, gunshot wound; IBS, intraoperative blood salvage; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation