Patient Blood Management Guidelines: Module 3

Medical

Technical report

Volume 2
Appendixes

This volume presents appendixes to *Technical report on medical patient blood management: Volume 1 – Review of the evidence and evidence-based recommendations for clinical practice*

Contents

Tables

Figures

Appendix A Literature searches

A1 Literature search – Question 1

Table A1.1 EMBASE.com search conducted 29 July 2010

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	128408
#2	'anemia'/exp OR anemia OR anaemia	219827
#3	'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR 'haemoglobin'/exp AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	75575
#4	#2 OR #3	280186
#5	'disease course'/exp OR 'disease course' OR 'disease attributes' OR 'disease development' OR 'disease evolution' OR 'disease progression' OR 'etiology'/exp OR aetiolog* OR etiolog* OR aetiopath* OR etiopath* OR 'natural history' OR 'risk factor'/exp OR 'risk factor'	9922890
#6	'adverse outcome'/exp OR (adverse AND (event* OR outcome*)) OR 'outcome assessment'/exp OR 'morbidity'/exp OR 'mortality'/exp OR morbidity OR incidence OR prevalence OR occurrence OR mortality OR death OR survival	3441530
#7	'functional status'/exp OR 'functional status' OR 'performance status' OR 'quality of life'/exp OR quality OR 'daily life activity'/exp OR (daily AND living) OR life OR adl OR 'functional assessment of chronic illness therapy' OR facit OR (functional AND assessment*) OR 'six minute walk test' OR 6mwt OR 'short form 36'/exp OR 'short form' OR 'sf 36' OR sf36 OR ecog OR 'karnofsky performance status'/exp OR karnofsky	2935405
#8	'heart infarction'/exp OR infarct* OR 'coronary artery acute occlusion' OR 'coronary artery occlusion' OR 'coronary occlusion' OR 'heart attack' OR 'stroke'/exp OR stroke OR 'cerebrovascular accident'/exp OR (cerebrovascular AND accident) OR ischem* OR 'cardiovascular disease'/exp OR reinfarct* OR 'heart arrhythmia'/exp OR arrhythmia* OR disrhythmia* OR (ectopic AND (rhythm OR beat* OR contraction)) OR 'heart aberrant conduction' OR (heart AND rhythm)	2613833
#9	#5 OR #6 OR #7 OR #8	12695292
#10	#4 AND #9	227515
#11	#4 AND #9 AND [1985–2011]/py	177113
#12	#1 AND #11	3128

Table A1.2 Cochrane library database search conducted 21 April 2010

#	Query	Results
#1	MeSH descriptor Anemia explode all trees	2821
#2	(anaemia OR anemia)	5606
#3	(#1 OR #2)	5852
#4	#3 limited to: “Cochrane Reviews”, “Other Reviews”, and “Technology Assessments”	623

A2 Literature search – Question 2

Table A2.1 EMBASE.com search for Level I evidence conducted 29 July 2010

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	128412
#2	'blood transfusion'/exp OR blood NEAR/4 transfus* OR 'erythrocyte transfusion' OR 'erythrocyte transfusions' OR 'red blood cell' NEAR/1 'transfusion' OR 'rbc' NEAR/1 'transfusion' OR 'red blood cell' NEAR/1 'transfusions' OR 'rbc' NEAR/1 'transfusions' OR 'red cell' NEAR/1 'transfusion' OR 'normocyte transfusion' OR 'red cell' NEAR/1 'transfusions' OR 'red blood cell' NEAR/1 'exchange' OR 'rbc' NEAR/1 'exchange' OR 'red cell' NEAR/3 'exchange' OR 'red cells' NEAR/3 'exchange'	120228
#3	'restrictive transfusion trigger' OR restrictive NEAR/3 transfus* OR 'low' NEAR/3 'transfusion' OR 'low' NEAR/3 'transfusions'	668
#4	liberal AND transfus* OR 'high' NEAR/3 'transfusion' OR 'high' NEAR/3 'transfusions'	788
#5	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	100123
#6	#2 OR #3 OR #4 OR #5	211369
#7	#2 OR #3 OR #4 OR #5 AND [1985–2011]/py	167384
#8	#1 AND #7	2497

Table A2.1 EMBASE.com search for Level II evidence conducted 16 May 2011

#	Query	Results
#1	'erythrocyte transfusion'/exp OR (blood:ab,ti OR erythrocyte:ab,ti OR 'red cell':ab,ti OR 'red blood cell':ab,ti OR rbc:ab,ti AND (transfus*:ab,ti OR infus*:ab,ti OR hypertransfus*:ab,ti OR retransfus*:ab,ti)) OR hemotransfus*:ab,ti OR haemotransfus*:ab,ti OR (transfus*:ab,ti OR retransfus*:ab,ti AND (trigger*:ab,ti OR level*:ab,ti OR threshold*:ab,ti OR rule*:ab,ti OR restrict*:ab,ti)) OR (transfusion:ab,ti AND (management:ab,ti OR practice*:ab,ti OR polic*:ab,ti OR strateg*:ab,ti OR guideline*:ab,ti OR indication*:ab,ti OR protocol*:ab,ti OR criteri*:ab,ti)) OR 'blood management':ab,ti OR 'management blood':ab,ti OR 'blood sparing':ab,ti OR 'cell salvage':ab,ti OR 'blood support':ab,ti OR 'blood requirement':ab,ti OR 'red cell management':ab,ti OR 'red cell sparing':ab,ti OR 'red cell support':ab,ti OR 'red cell requirement':ab,ti OR (blood NEXT/1 need):ab,ti OR leukodeplet*:ab,ti OR leukoreduc*:ab,ti OR leucodepl*:ab,ti OR leucodeplet*:ab,ti OR leucoreduc*:ab,ti OR leukofiltrat*:ab,ti OR leucofiltra*:ab,ti OR ((leukocyte* OR leucocyte*) NEXT/2 (remov* OR deplet* OR reduc* OR poor OR filtrat*)):ab,ti OR ((iron NEXT/5 (intravenous* OR iv)):ab,ti AND transfus*:ab,ti) OR ('blood transfusion'/exp OR 'blood component therapy'/exp NOT ('exchange blood transfusion'/exp OR 'plasma transfusion'/exp OR 'granulocyte transfusion'/exp OR 'amnioinfusion'/exp OR 'leukocyte transfusion'/exp OR 'intrauterine blood transfusion'/exp OR 'thrombocyte transfusion'/exp OR 'lymphocyte transfusion'/exp)) OR ('blood transfusion'/exp OR 'blood component therapy'/exp AND 'erythrocyte'/exp AND ('red cell':ab,ti OR 'red blood cell':ab,ti OR erythrocyte*:ab,ti)) OR 'red cell':ab,ti OR 'red blood cell':ab,ti OR erythrocyte*:ab,ti OR rbc*:ab,ti	337496
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR	2312114

#	Query	Results
	'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	
#3	#1 AND #2	49619
#4	#1 AND #2 AND [1–9-2009]/sd NOT [29–7-2010]/sd AND [2007–2011]/py	3506

Table A2.1 EMBASE.com search for Level III evidence conducted 6 June 2011

#	Query	Results
#1	'blood transfusion'/exp OR blood NEAR/4 transfus* OR 'erythrocyte transfusion' OR 'erythrocyte transfusions' OR 'red blood cell' NEAR/1 'transfusion' OR 'rbc' NEAR/1 'transfusion' OR 'red blood cell' NEAR/1 'transfusions' OR 'rbc' NEAR/1 'transfusions' OR 'red cell' NEAR/1 'transfusion' OR 'normocyte transfusion' OR 'red cell' NEAR/1 'transfusions' OR 'red blood cell' NEAR/1 'exchange' OR 'rbc' NEAR/1 'exchange' OR 'red cell' NEAR/3 'exchange' OR 'red cells' NEAR/3 'exchange'	131380
#2	'restrictive transfusion trigger' OR restrictive NEAR/3 transfus* OR 'low' NEAR/3 'transfusion' OR 'low' NEAR/3 'transfusions'	862
#3	liberal AND transfus* OR 'high' NEAR/3 'transfusion' OR 'high' NEAR/3 'transfusions'	947
#4	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	111558
#5	#1 OR #2 OR #3 OR #4	232567
#6	mortality:ab,ti OR death*:ab,ti OR died:ab,ti OR ((cardiac OR heart OR coronary OR myocard*) NEXT/3 (infarct* OR attack OR occlusion)):ab,ti OR stroke:ab,ti OR ((cerebr* OR brain OR cranial) NEXT/3 (accident OR ischemia OR ischaemia OR infarct* OR hemorrhage OR haemorrhage)):ab,ti OR 'quality of life':ab,ti OR qol:ab,ti OR 'performance status':ab,ti OR 'functional status':ab,ti OR 'activities of daily living':ab,ti OR adl:ab,ti OR barthel:ab,ti OR karnofsky:ab,ti OR katz:ab,ti OR nottingham:ab,ti OR 'well being':ab,ti OR wellbeing:ab,ti OR disability:ab,ti OR 'health utility':ab,ti OR 'walk test':ab,ti OR 15d:ab,ti OR dasi:ab,ti OR ecog:ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR facit:ab,ti OR fact:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR 6mwt:ab,ti OR nhp:ab,ti OR qwb:ab,ti OR 'rand 36':ab,ti OR rand36:ab,ti OR 'sf 12':ab,ti OR sf12:ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'circulatory overload':ab,ti OR taco:ab,ti OR 'acute lung injury':ab,ti OR trali:ab,ti OR (hemolytic NEXT/4 reaction*):ab,ti OR 'transfusion reaction':ab,ti OR infection:ab,ti OR ('graft versus host' NEXT/2 (disease OR reaction)):ab,ti OR anaphyla*:ab,ti	2282519
#7	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	5774373
#8	#5 AND #6 AND #7	29531
#9	#5 AND #6 AND #7 AND [1–1-1985]/sd NOT [31–12–1994]/sd	3510
#10	#5 AND #6 AND #9 AND [1–1-1995]/sd NOT [31–10–2008]/sd	16619
#11	#5 AND #6 AND #9 AND [1–1-1995]/sd NOT [31–10–2008]/sd AND [medline]/lim	13990
#12	#10 NOT #11	2629

#	Query	Results
#13	#5 AND #6 AND #7 AND [1–11–2008]/sd NOT [29–7-2010]/sd	4816
#14	#9 OR #12 OR #13	10955

Table A2.1 Additional EMBASE.com search for Level III evidence with organ failure terms conducted 12 September 2011

#	Query	Results
#1	'blood transfusion'/exp OR blood NEAR/4 transfus* OR 'erythrocyte transfusion' OR 'erythrocyte transfusions' OR 'red blood cell' NEAR/1 'transfusion' OR 'rbc' NEAR/1 'transfusion' OR 'red blood cell' NEAR/1 'transfusions' OR 'rbc' NEAR/1 'transfusions' OR 'red cell' NEAR/1 'transfusion' OR 'normocyte transfusion' OR 'red cell' NEAR/1 'transfusions' OR 'red blood cell' NEAR/1 'exchange' OR 'rbc' NEAR/1 'exchange' OR 'red cell' NEAR/3 'exchange' OR 'red cells' NEAR/3 'exchange'	134189
#2	'restrictive transfusion trigger' OR restrictive NEAR/3 transfus* OR 'low' NEAR/3 'transfusion' OR 'low' NEAR/3 'transfusions'	901
#3	liberal AND transfus* OR 'high' NEAR/3 'transfusion' OR 'high' NEAR/3 'transfusions'	984
#4	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	115522
#5	#1 OR #2 OR #3 OR #4	238967
#6	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	5872351
#7	'organ failure':ab,ti OR 'organ dysfunction':ab,ti	18675
#8	#5 AND #6 AND #7	697
#13	#5 AND #6 AND #7 AND [1–1-1985]/sd NOT [29–7-2010]/sd	564

Table A2.2 Cochrane library: search conducted 2 August 2010

#	Query	Results
#1	MeSH descriptor Erythrocyte Transfusion explode all trees	414
#2	MeSH descriptor Blood Transfusion explode all trees	2921
#3	blood NEAR/3 transfusion	4797
#4	"erythrocyte transfusion" OR "erythrocyte transfusions"	509
#5	("red blood cell" OR rbc) NEAR/1 transfusion*	166
#6	"red cell" NEAR/1 transfusion*	3
#7	"normocyte transfusion" OR "normocyte transfusions"	0
#8	("red blood cell" OR rbc) NEAR/1 exchange	2

#	Query	Results
#9	("red cell" OR "red cells") NEAR/3 exchange	4
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	5313
#11	(restrictive AND transfus*)	57
#12	(restrictive OR low) NEAR/3 transfusion*	232
#13	(#11 OR #12)	253
#14	(liberal AND transfus*)	39
#15	(liberal OR high) NEAR/3 transfusion*	170
#16	(#14 OR #15)	182
#17	"transfusion threshold" OR "transfusion thresholds"	45
#18	transfusion NEAR/1 trigger*	61
#19	"transfusion strategy" OR "transfusion strategies"	40
#20	"transfusion policy" OR "transfusion policies"	23
#21	"transfusion practice" OR "transfusion practices"	57
#22	"transfusion protocol" OR "transfusion protocols"	55
#23	transfusion NEAR/1 guideline*	34
#24	"hemoglobin threshold" OR "hemoglobin trigger"	5
#25	"haemoglobin threshold" OR "haemoglobin trigger"	6
#26	"hb threshold" OR "hb trigger"	8
#27	"haemoglobin thresholds" OR "haemoglobin triggers"	2
#28	"hb thresholds" OR "hb triggers"	2
#29	(#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)	1310
#30	(#10 OR #13 OR #16 OR #29)	6647
#31	#30 limited to: “Cochrane Reviews”, “Other Reviews”, and “Technology Assessments”	567
#32	#32 limited to: “Clinical Trials”	4367

A3 Literature search – Question 3

Table A3.1 EMBASE.com search for Level I studies conducted 29 July 2010

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	128412
#2	'erythropoietin'/exp OR erythropoietin OR 'recombinant erythropoietin'/exp OR erthropoietin OR 'erythropoiesis stimulating' OR 'erythropoietic factor' OR hematopoietin OR hemopoietin OR haematopoietin OR haemopoietin OR 'dynepo'/exp OR 'epoch'/exp OR 'epoconn'/exp OR 'epoetin'/exp OR epog?n OR epoietin OR epoxitin OR darbepoetin OR eprex OR erantin OR erypo OR espo OR exprex OR globuren OR hemax OR marogen OR neorecormon OR procrit OR recormon OR recormone OR rhuepo OR 'rhu epo' OR 'r hu epo'	37195
#3	'iron'/exp OR iron	196579
#4	#2 OR #3	226930
#5	#2 OR #3 AND [1985–2011]/py	174729
#6	#1 AND #5	1593

Table A3.1 EMBASE.com search for Level II studies conducted 24 October 2010

#	Query	Results
#1	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2208314
#2	'erythropoietin'/exp OR erythropoietin OR 'recombinant erythropoietin'/exp OR erthropoietin OR 'erythropoiesis stimulating factor' OR 'erythropoietic factor' OR hematopoietin OR hemopoietin OR haematopoietin OR haemopoietin OR 'dynepo'/exp OR 'epoch'/exp OR 'epoconn'/exp OR 'epoetin'/exp OR epog?n OR epoietin OR epoxitin OR eprex OR erantin OR erypo OR espo OR exprex OR globuren OR hemax OR marogen OR neorecormon OR procrit OR recormon OR recormone OR 'krn 5702' OR krn5702 OR 'snb 5001' OR snb5001 OR 'tyb 5220' OR tyb5220 OR rhuepo OR 'rhu epo' OR 'r hu epo'	37310
#3	#1 AND #2	8247
#4	'iron therapy'/exp OR (iron AND (supplement* OR therap* OR replace*))	173547
#5	'adverse outcome'/exp OR 'outcome assessment'/exp OR 'morbidity'/exp OR 'mortality'/exp OR morbidity:ab,ti OR incidence:ab,ti OR prevalence:ab,ti OR occurrence:ab,ti OR mortality:ab,ti OR death:ab,ti OR survival:ab,ti OR 'quality of life'/exp OR qol:ab,ti OR 'quality of life':ab,ti OR 'quality of wellbeing':ab,ti OR 'health related quality':ab,ti OR hrqol:ab,ti OR qaly*:ab,ti OR 'quality adjusted':ab,ti OR 'adjusted life':ab,ti OR 'blood transfusion'/exp OR ('frequency' NEAR/5 'transfusion'):ab,ti OR ('frequency' NEAR/5 'transfusions'):ab,ti OR 'transfusion frequency':ab,ti OR 'transfusion rate':ab,ti OR 'transfusion rates':ab,ti OR ('rate' NEAR/5 'transfusion'):ab,ti OR ('rates' NEAR/5 'transfusion'):ab,ti OR 'transfusion requirement':ab,ti OR 'transfusion requirements':ab,ti OR 'transfusion indication':ab,ti OR 'transfusion indications':ab,ti OR ('indications' NEAR/5 'transfusion'):ab,ti OR ('indications' NEAR/5 'transfusions'):ab,ti OR ('indication' NEAR/5 'transfusion'):ab,ti OR ('indication' NEAR/5 'transfusions'):ab,ti OR 'health economics'/exp OR 'economic aspect'/exp OR 'biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'health care cost'/exp OR economic*:ab,ti OR	3573364

#	Query	Results
	pharmacoeconomic*:ab,ti OR cost*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR 'burden of illness':ab,ti OR 'hospitalization'/exp OR 'length of stay'/exp OR hospitaliz*:ab,ti OR hospitalis*:ab,ti OR ('length' NEAR/3 'stay'):ab,ti OR 'hospital stay':ab,ti OR 'intensive care unit'/exp OR 'intensive care unit':ab,ti OR icu:ab,ti OR 'intensive care units':ab,ti OR 'close attention unit':ab,ti OR 'close attention units':ab,ti OR 'intensive care department':ab,ti OR 'intensive care departments':ab,ti OR 'special care unit':ab,ti OR 'special care units':ab,ti OR 'critical care unit':ab,ti OR 'critical care units':ab,ti OR 'hospital admission'/exp OR 'hospital readmission'/exp OR 'hospital admission':ab,ti OR 'hospital admittance':ab,ti OR 'patient admission':ab,ti OR readmission:ab,ti OR rehospitalization:ab,ti OR rehospitalisation:ab,ti	
#6	'thromboembolism'/exp OR thromb* OR embol* OR microembol* OR 'stroke'/exp OR stroke OR 'infarction'/exp OR infarct* OR mi OR occlusion* OR 'heart attack' OR 'deep vein thrombosis'/exp OR dvt OR 'lung embolism'/exp OR pe	1631436
#7	'functional status'/exp OR 'functional status' OR 'functional capacity' OR aqol OR barthel OR 15d OR dasi OR ecog OR 'eastern cooperative oncology group' OR eq5d OR 'eq 5d' OR 'functional assessment of chronic illness therapy' OR facit OR utilit* OR hui2 OR hui3 OR iadl OR karnofsky OR katz OR walk* OR 6mwt OR '6 mwt' OR mqol OR nhp OR 'nationwide health properties' OR 'quality of well being scale' OR qwb OR 'rand 36' OR 'sf 12' OR 'sf 36'	472329
#8	#5 OR #6 OR #7	5114415
#9	#1 AND #4 AND #8	7094
#10	#1 AND #2 AND [2006–2011]/py	3555
#11	#9 OR #10	10043
#12	#9 OR #10 AND [1985–2011]/py	9776

Table A3.2 Cochrane library database search for Level I studies conducted 21 April 2010

#	Query	Results
#1	MeSH descriptor Erythropoietin explode all trees	1370
#2	(erthropoietin OR "erythropoiesis stimulating factor")	4
#3	"erythropoietic NEAR/1 factor"	0
#4	(hematopoietin OR hemopoietin)	2
#5	(haematopoietin OR haemopoietin)	1
#6	(dynepo OR epoch OR epoconn OR epoetin OR epog?n)	904
#7	(epoietin OR epoxitin OR eprex OR erantin OR erypo)	65
#8	(espo OR exprex OR globuren OR hemax OR marogen)	35
#9	(neorecormon OR procrit OR recormon OR recormone)	52
#10	(rHuEPO OR "rHu EPO" OR "r Hu EPO")	396
#11	MeSH descriptor Iron explode all trees	1445
#12	iron	3675
#13	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)	5288
#14	#13 limited to: “Cochrane Reviews”, “Other Reviews”, and “Technology Assessments”	301

Table A3.2 Cochrane library database search for Level II studies conducted 21 April 2010

#	Query	Results
#1	MeSH descriptor Erythropoietin explode all trees	1387
#2	(erthropoietin OR "erythropoiesis stimulating factor")	4
#3	erythropoietic NEAR/1 factor	0
#4	(hematopoietin OR hemopoietin)	2
#5	(haematopoietin OR haemopoietin)	1
#6	(dynepo OR epoch OR epoconn OR epoetin OR epog?n)	914
#7	(epoietin OR epoxitin OR eprex OR erantin OR erypo)	65
#8	(espo OR exprex OR globuren OR hemax OR marogen)	35
#9	(neorecormon OR procrit OR recormon OR recormone)	52
#10	(rHuEPO OR "rHu EPO" OR "r Hu EPO")	399
#11	iron AND (supplement* OR therap* OR replace*)	2690
#12	MeSH descriptor Morbidity explode all trees	9835
#13	MeSH descriptor Mortality explode all trees	8969
#14	MeSH descriptor Quality of Life explode all trees	11382
#15	MeSH descriptor Stroke explode all trees	3600
#16	MeSH descriptor Myocardial Infarction explode all trees	7452
#17	MeSH descriptor Venous Thrombosis explode all trees	2094
#18	MeSH descriptor Pulmonary Embolism explode all trees	799
#19	'adverse outcome' OR 'adverse outcomes' OR 'adverse event' OR 'adverse events' OR 'outcome assessment' OR morbidity OR mortality OR death OR survival OR 'quality of life' OR qol OR 'quality of wellbeing' OR 'health related quality' OR hrqol OR qaly OR 'quality adjusted' OR 'adjusted life' OR transfus*	76211
#20	'functional status' OR 'functional capacity' OR aqol OR barthel OR activit* OR 15d OR dasi OR ecog OR 'eastern cooperative oncology group' OR eq5d OR 'eq 5d' OR 'functional assessment of chronic illness therapy' OR facit OR utilit* OR hui2 OR hui3 OR iadl OR karnofsky OR katz OR walk* OR 6mwt OR '6 mwt' OR mqol OR nhp OR 'nationwide health properties' OR 'quality of well being scale' OR qwb OR 'rand 36' OR 'sf 12' OR 'sf 36'	70069
#21	thrombo* OR embol* OR microembol* OR stroke OR infarct* OR MI OR occlusion* OR 'heart attack' OR dvt OR pe	62912
#22	(#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)	184872
#23	(#11 AND #22), from 1985 to 2010	974
#24	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10), from 2006 to 2010	567
#25	(#23 OR #24)	1484
#26	#25 limited to: “Clinical Trials”	1136

A4 Literature search – Question 4

Table A4.1 EMBASE.com search for Level I studies conducted 29 July 2010

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	128412
#2	'blood component therapy'/exp OR 'blood transfusion'/exp OR 'transfusion'/exp OR transfus* OR 'blood exchange' OR 'blood infusion' OR 'blood replacement' OR hemotherapy OR hematherapy OR hematotherapy OR haemotherapy OR haematherapy OR haematotherapy OR multitransfusion OR polytransfusion OR retransfus*	237112
#3	'blood component'/exp OR 'blood component' OR 'blood components' OR 'blood product' OR 'blood products' OR 'transfusion product' OR 'transfusion products' OR 'blood constituent' OR 'blood constituents'	31534
#4	'fresh frozen plasma'/exp OR 'plasma'/exp OR 'fresh frozen plasma' OR ffp	70596
#5	'plasma transfusion'/exp OR 'plasma transfusion' OR 'plasma infusion' OR 'serum transfusion'	2222
#6	'cryoprecipitate'/exp OR 'cryoprecipitate coagulum' OR cryoprecipitate OR 'cryo precipitate'	2679
#7	'fibrinogen'/exp OR fibrinogen OR 'factor 1' OR 'factor i'	135501
#8	'thrombocyte transfusion'/exp OR ('thrombocyte'/exp AND ('blood transfusion'/exp OR 'transfusion'/exp)) OR 'platelet' NEAR/1 'transfusion' OR 'platelet' NEAR/1 'transfusions' OR 'transfusion' NEAR/3 'platelet' OR 'transfusion' NEAR/3 'platelets' OR 'thrombocyte transfusion' OR 'thrombocytic transfusion'	11994
#9	#3 OR #4 OR #6 OR #7	231087
#10	#2 AND #9	34289
#11	#5 OR #8 OR #10	37768
#12	#5 OR #8 OR #10 AND [1970–2011]/py	36838
#13	#1 AND #12	681

Table A5.1 EMBASE.com search for Level II studies conducted 29 July 2010

#	Query	Results
#1	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2198418
#2	'blood component therapy'/exp OR 'blood transfusion'/exp OR 'transfusion'/exp OR transfus* OR 'blood exchange' OR 'blood infusion' OR 'blood replacement' OR hemotherapy OR hematherapy OR hematotherapy OR haemotherapy OR haematherapy OR haematotherapy OR multitransfusion OR polytransfusion OR retransfus*	240204
#3	'blood component'/exp OR 'blood component' OR 'blood components' OR 'blood product' OR 'blood products' OR 'transfusion product' OR 'transfusion products' OR 'blood constituent' OR 'blood constituents'	32497

#	Query	Results
#4	'fresh frozen plasma'/exp OR 'plasma'/exp OR 'fresh frozen plasma' OR ffp	72993
#5	'plasma transfusion'/exp OR 'plasma transfusion' OR 'plasma infusion' OR 'serum transfusion'	2257
#6	'cryoprecipitate'/exp OR 'cryoprecipitate coagulum' OR cryoprecipitate OR 'cryo precipitate'	2753
#7	'fibrinogen'/exp OR fibrinogen OR 'factor 1' OR 'factor i'	137876
#8	'thrombocyte transfusion'/exp OR ('thrombocyte'/exp AND ('blood transfusion'/exp OR 'transfusion'/exp)) OR 'platelet' NEAR/1 'transfusion' OR 'platelet' NEAR/1 'transfusions' OR 'transfusion' NEAR/3 'platelet' OR 'transfusion' NEAR/3 'platelets' OR 'thrombocyte transfusion' OR 'thrombocytic transfusion'	12662
#9	#3 OR #4 OR #6 OR #7	236388
#10	#2 AND #9	35612
#11	#5 OR #8 OR #10	39269
#12	#5 OR #8 OR #10 AND [1970–2011]/py	36838
#13	#1 AND #12	7710

Table A5.1 EMBASE.com search for Level III-IV studies of platelet transfusions conducted 29 April 2011

#	Query	Results
#1	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	5734332
#2	'thrombocyte transfusion'/exp OR ('thrombocyte'/exp AND ('blood transfusion'/exp OR 'transfusion'/exp)) OR 'platelet' NEAR/1 'transfusion' OR 'platelet' NEAR/1 'transfusions' OR 'transfusion' NEAR/3 'platelet' OR 'transfusion' NEAR/3 'platelets' OR 'thrombocyte transfusion' OR 'thrombocytic transfusion'	13588
#3	#1 AND #2 AND [1–1-1970]/sd NOT [29–7-2010]/sd AND ([article]/lim OR [article in press]/lim) AND [english]/lim	4204

Table A5.2 Cochrane library database search conducted 21 April 2010

#	Query	Results
#1	MeSH descriptor Blood Component Transfusion explode all trees	729
#2	MeSH descriptor Blood Transfusion explode all trees	2864
#3	*transfus*	7515
#4	"blood exchange" OR "blood infusion"	47
#5	"blood replacement"	67
#6	hemotherapy OR hematherapy OR hematotherapy	61
#7	haemotherapy OR haematherapy OR haematotherapy	7
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)	7758

#	Query	Results
#9	"blood component" OR "blood components"	459
#10	"blood product" OR "blood products"	688
#11	"transfusion product" OR "transfusion products"	8
#12	"blood constituent" OR "blood constituents"	14
#13	(#9 OR #10 OR #11 OR #12)	1104
#14	(#8 AND #13)	721
#15	MeSH descriptor Plasma explode all trees	327
#16	"fresh frozen plasma" OR FFP	382
#17	(#15 OR #16)	624
#18	(#8 AND #17)	312
#19	"plasma transfusion"	33
#20	"plasma infusion" OR "serum transfusion"	19
#21	(#18 OR #19 OR #20)	336
#22	cryoprecipitate OR "cryo precipitate"	67
#23	(#22 AND #8)	39
#24	fibrinogen OR "factor 1" OR "factor I"	4730
#25	(#8 AND #24)	311
#26	MeSH descriptor Platelet Transfusion explode all trees	228
#27	MeSH descriptor Blood Platelets explode all trees	1435
#28	(#8 AND #27)	140
#29	platelet* NEAR/3 transfusion*	599
#30	"thrombocyte transfusion" OR "thrombocytic transfusion"	41
#31	(#26 OR #28 OR #29 OR #30)	668
#32	(#14 OR #21 OR #23 OR #25 OR #31)	1638
#33	#32 limited to: “Cochrane Reviews”, “Other Reviews”, and “Technology Assessments”	171
#34	#32 limited to: “Clinical Trials”	1344

A6 Literature search – Question 5

Table A6.1 EMBASE.com search for Level I studies conducted 29 July 2010

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	128412
#2	'transfusion'/exp OR 'blood transfusion'/exp OR transfus* OR 'blood exchange' OR 'blood infusion' OR 'blood replacement' OR 'blood retransfusion' OR hemotherapy OR hematherapy OR hematotherapy OR haemotherapy OR haematherapy OR haematotherapy OR multitransfusion OR polytransfusion OR retransfusion OR 'transfusion blood' OR 'transfusion therapy'	237068
#3	'fresh frozen plasma'/exp OR 'plasma'/exp OR 'plasma transfusion'/exp OR 'fresh frozen plasma' OR ffp OR 'plasma infusion' OR 'serum transfusion'	71764
#4	'international normalized ratio'/exp OR 'prothrombin time'/exp OR 'partial thromboplastin time'/exp OR 'thromboplastin time'/exp OR 'thrombotest'/exp OR 'international standard unit'/exp OR 'russell viper venom' OR 'international normalized ratio' OR inr OR 'international normalised ratio' OR 'international sensitivity index' OR 'prothrombin' NEAR/1 'time' OR 'thromboplastin' NEAR/1 'time' OR thrombotest OR 'prothrombin test' OR 'prothrombine time' OR 'protrombin time' OR 'howell test' OR 'smith test' OR 'quick test' OR ptt OR aptt	35564
#5	#2 AND #3 AND #4	905
#6	'cryoprecipitation'/exp OR 'cryoprecipitate coagulum' OR cryoprecipitate OR 'cryo precipitate'	3118
#7	'fibrinogen'/exp OR 'fibrinogen blood level'/exp OR fibrinogen OR 'factor 1' OR 'factor i'	135501
#8	#2 AND #6 AND #7	327
#9	'thrombocyte concentrate'/exp OR 'thrombocyte transfusion'/exp OR ('thrombocyte'/exp AND ('blood transfusion'/exp OR transfus*)) OR 'thrombocyte concentrate' OR 'thrombocyte concentrates' OR 'platelet concentrate' OR 'platelet concentrates' OR 'platelet' NEAR/1 'transfusion' OR 'platelet' NEAR/1 'transfusions' OR 'transfusion' NEAR/3 'platelet' OR 'transfusion' NEAR/3 'platelets' OR 'thrombocyte transfusion' OR 'thrombocytic transfusion'	15363
#10	'thrombocyte count'/exp OR 'thrombocyte count' OR 'thrombocytic count' OR 'thrombocyte counts' OR 'thrombocytic counts' OR 'thrombocyte number' OR 'thrombocyte numbers' OR 'thrombocyte counting' OR 'platelet counting' OR 'platelet count' OR 'platelet counts' OR 'platelet number' OR 'platelet numbers'	35929
#11	#2 AND #9 AND #10	2908
#12	#5 OR #8 OR #11	3911
#13	#5 OR #8 OR #11 AND [1970–2011]/py	3900
#14	#1 AND #13	64

Table A6.1 EMBASE.com search for Level II studies conducted 20 October 2010

#	Query	Results
#1	'transfusion'/exp OR 'blood transfusion'/exp OR transfus* OR 'blood exchange' OR 'blood infusion' OR 'blood replacement' OR 'blood retransfusion' OR hemotherapy OR hematherapy OR hematotherapy OR haemotherapy OR haematherapy OR haematotherapy OR multitransfusion OR polytransfusion OR retransfusion OR 'transfusion blood' OR 'transfusion therapy'	242440
#2	'fresh frozen plasma'/exp OR 'plasma'/exp OR 'plasma transfusion'/exp OR 'fresh frozen plasma' OR	74953

#	Query	Results
	ffp OR 'plasma infusion' OR 'serum transfusion'	
#3	'international normalized ratio'/exp OR 'prothrombin time'/exp OR 'partial thromboplastin time'/exp OR 'thromboplastin time'/exp OR 'thrombotest'/exp OR 'international standard unit'/exp OR 'russell viper venom' OR 'international normalized ratio' OR inr OR 'international normalised ratio' OR 'international sensitivity index' OR 'prothrombin' NEAR/1 'time' OR 'thromboplastin' NEAR/1 'time' OR thrombotest OR 'prothrombin test' OR 'prothrombine time' OR 'protrombin time' OR 'howell test' OR 'smith test' OR 'quick test' OR ptt OR aptt	36586
#4	#1 AND #2 AND #3	961
#5	'cryoprecipitation'/exp OR 'cryoprecipitate coagulum' OR cryoprecipitate OR 'cryo precipitate'	3200
#6	'fibrinogen'/exp OR 'fibrinogen blood level'/exp OR fibrinogen OR 'factor 1' OR 'factor i'	138498
#7	#1 AND #5 AND #6	341
#8	'thrombocyte concentrate'/exp OR 'thrombocyte transfusion'/exp OR ('thrombocyte'/exp AND ('blood transfusion'/exp OR transfus*)) OR 'thrombocyte concentrate' OR 'thrombocyte concentrates' OR 'platelet concentrate' OR 'platelet concentrates' OR 'platelet' NEAR/1 'transfusion' OR 'platelet' NEAR/1 'transfusions' OR 'transfusion' NEAR/3 'platelet' OR 'transfusion' NEAR/3 'platelets' OR 'thrombocyte transfusion' OR 'thrombocytic transfusion'	16174
#9	'thrombocyte count'/exp OR 'thrombocyte count' OR 'thrombocytic count' OR 'thrombocyte counts' OR 'thrombocytic counts' OR 'thrombocyte number' OR 'thrombocyte numbers' OR 'thrombocyte counting' OR 'platelet counting' OR 'platelet count' OR 'platelet counts' OR 'platelet number' OR 'platelet numbers'	37099
#10	#1 AND #8 AND #9	3064
#11	#4 OR #7 OR #10	4124
#12	#4 OR #7 OR #10 AND [1970–2011]/py	4113
#13	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	5557937
#14	#12 AND #13	2443

Table A6.2 Cochrane library database search conducted 21 April 2011

#	Query	Results
#1	MeSH descriptor Blood Transfusion explode all trees	2864
#2	*transfus*	7515
#3	"blood exchange" OR "blood infusion"	47
#4	"blood replacement" OR "blood retransfusion"	76
#5	hemotherapy OR hematherapy OR hematotherapy	61
#6	haemotherapy OR haematherapy OR haematotherapy	7
#7	multitransfusion OR polytransfusion OR retransfusion	71

#	Query	Results
#8	"transfusion blood" OR "transfusion therapy"	239
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	7758
#10	MeSH descriptor Plasma explode all trees	327
#11	"fresh frozen plasma" OR FFP	382
#12	"plasma transfusion"	33
#13	"plasma infusion" OR "serum transfusion"	19
#14	(#10 OR #11 OR #12 OR #13)	647
#15	MeSH descriptor International Normalized Ratio explode all trees	302
#16	MeSH descriptor Prothrombin Time explode all trees	374
#17	MeSH descriptor Partial Thromboplastin Time explode all trees	393
#18	"international normalized ratio" OR inr	836
#19	"international normalised ratio"	145
#20	"International Sensitivity Index" OR isi	927
#21	(prothrombin NEAR/1 time) OR pt OR Thrombotest	14400
#22	"prothrombin test" OR "prothrombine time" OR "protrombin time"	13
#23	"howell test" OR "smith test" OR "Quick Test"	24
#24	"Russell Viper Venom Time" OR dRVVT OR RVVT	9
#25	"partial thromboplastin time" OR ptt OR aptt	1155
#26	(#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)	16472
#27	(#14 AND #26)	98
#28	(#9 AND #27)	66
#29	cryoprecipitate	67
#30	cryoprecipitate OR "cryo precipitate"	67
#31	(#14 OR #29 OR #30)	682
#32	MeSH descriptor Fibrinogen explode all trees	1359
#33	fibrinogen OR "factor 1" OR "factor I"	4730
#34	(#32 OR #33)	4774
#35	(#31 AND #34)	74
#36	(#9 AND #35)	51
#37	MeSH descriptor Platelet Transfusion explode all trees	228
#38	MeSH descriptor Blood Platelets explode all trees	1435
#39	MeSH descriptor Blood Transfusion explode all trees	2864
#40	(#38 AND #39)	101
#41	"thrombocyte concentrate" OR "thrombocyte concentrates"	16

#	Query	Results
#42	"platelet concentrate" OR "platelet concentrates"	184
#43	platelet* NEAR/3 transfusion*	599
#44	"thrombocyte transfusion" OR "thrombocytic transfusion"	41
#45	(#37 OR #40 OR #41 OR #42 OR #43 OR #44)	731
#46	MeSH descriptor Platelet Count explode all trees	1021
#47	"thrombocyte count" OR "thrombocytic count"	143
#48	"thrombocyte counts" OR "thrombocytic counts"	11
#49	"thrombocyte number" OR "thrombocyte numbers"	1
#50	"thrombocyte counting" OR "platelet counting"	11
#51	"platelet count" OR "platelet counts"	2259
#52	"platelet number" OR "platelet numbers"	79
#53	(#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)	2378
#54	(#45 AND #53)	232
#55	(#9 AND #54)	228
#56	(#28 OR #36 OR #55)	304
#57	#56 limited to: “Cochrane Reviews”, “Other Reviews”, and “Technology Assessments”	33
#58	#56 limited to: “Clinical Trials”	255

A7 Literature search – Question 6

Table A7.1 EMBASE.com search for Level I studies conducted 9 August 2010

#	Query	Results
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	128773
#2	(chronic* OR regular*) NEAR/3 transfus* OR 'thalassemia'/exp OR thalas* OR 'myelodysplastic syndrome'/exp OR 'bone marrow dysplasia' OR mds OR myelodysplas* OR 'aplastic anemia'/exp OR ('anemia'/exp OR anemia OR anaemia AND (aplast* OR hypoplast* OR aregenerative OR 'toxic paralytic')) OR 'blood aplasia' OR 'congenital erythroblastopenia' OR 'congenital erythroid hypoplasia' OR 'progressive hypocythemia' OR myeloproliferat* OR 'myelo proliferative' OR ('bone marrow' AND (failure OR fibrosis OR deficien* OR deplet* OR dysfunction* OR insufficien*)) OR myelofibro* OR myelosclero* OR (anemia OR anaemia) NEAR/3 (hereditary OR congenital) OR chronic* NEXT/1 (anemi* OR anaemi*)	410668
#3	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	100340
#4	#1 AND #2 AND #3	113

Table A7.1 EMBASE.com search for Level II and III studies conducted 20 January 2011

#	Query	Results
#1	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2245156
#2	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	5632770
#3	#1 OR #2	6594007
#4	(chronic* OR regular*) NEAR/3 transfus* OR 'thalassemia'/exp OR thalas* OR 'myelodysplastic syndrome'/exp OR 'bone marrow dysplasia' OR mds OR myelodysplas* OR 'aplastic anemia'/exp OR ('anemia'/exp OR anemia OR anaemia AND (aplast* OR hypoplast* OR aregenerative OR 'toxic paralytic')) OR 'blood aplasia' OR 'congenital erythroblastopenia' OR 'congenital erythroid hypoplasia' OR 'progressive hypocythemia' OR myeloproliferat* OR 'myelo proliferative' OR ('bone marrow' AND (failure OR fibrosis OR deficien* OR deplet* OR dysfunction* OR insufficien*)) OR myelofibro* OR myelosclero* OR (anemia OR anaemia) NEAR/3 (hereditary OR congenital) OR chronic* NEXT/1 (anemi* OR anaemi*)	428292
#5	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum	106439

#	Query	Results
	haemoglobin'	
#6	#3 AND #4 AND #5	7526

Table A7.3 Cochrane library database search conducted 9 August 2010

#	Query	Results
#1	MeSH descriptor Thalassemia explode all trees	185
#2	thalas* OR 'bone marrow dysplasia' OR mds OR myelodysplas*	1124
#3	transfus* AND (chronic* OR regular*)	756
#4	(anaemia OR anemia) NEAR/3 (hereditary OR congenital)	12
#5	('anemia'/exp OR anemia OR anaemia AND (aplast* OR hypoplast* OR aregenerative OR 'toxic paralytic'))	5609
#6	'blood aplasia' OR 'congenital erythroblastopenia' OR 'congenital erythroid hypoplasia' OR 'progressive hypocythemia' OR myeloproliferat* OR 'myelo proliferative' OR ('bone marrow' AND (failure OR fibrosis OR deficien* OR deplet* OR dysfunction* OR insufficien*)) OR myelofibro* OR myelosclero*	106
#7	chronic NEAR/1 (anemi* OR anaemi*)	63
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)	7068
#9	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*)	224
#10	hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)	10011
#11	'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	1
#12	(#9 OR #10 OR #11)	10152
#13	(#8 AND #12)	2133
#14	#13 limited to: “Cochrane Reviews”, “Other Reviews”, and “Technology Assessments”	259
#15	#13 limited to: “Clinical Trials”	1879

Appendix B Excluded studies

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

B1 Studies excluded from question 1

For the Level I search, all citations within a single database were examined for all indications. For the Level II search, specific indications were examined within a large database, so there is a separate subset of the database for each indication.

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

Stein, J. M., F. Hartmann, H. J. Cordes, and A. U. Dignass, 2009, Pathophysiological-based diagnosis and therapy of iron-deficient anaemia in inflammatory bowel disease: Zeitschrift fur Gastroenterologie, v. 47, no. 2, p. 228–236.

Abstract only

Caocci, G., F. Efficace, M. Vignetti, F. Mandelli, P. Fazi, A. Ledda, and G. La Nasa, 2009, Health-related quality of life of patients with myelodysplastic syndromes - A systematic review from 1980 to 2008: Haematologica, v. 94, p. 111.

No relevant results reported

Huang, J. T., and J. Means, 2010, The frequency and significance of Iron-Deficiency anemia in patients with selected concurrent illness: Internet Journal of Internal Medicine, v. 8, no. 1.

Pinchon, D. J., S. J. Stanworth, C. Doree, S. Brunskill, and D. R. Norfolk, 2009, Quality of life and use of red cell transfusion in patients with myelodysplastic syndromes. A systematic review: American Journal of Hematology, v. 84, no. 10, p. 671–677.

Superseded

Strippoli, G. F., C. Manno, F. P. Schena, and J. C. Craig, 2003, Haemoglobin and haematocrit targets for the anaemia of chronic renal disease: Cochrane database of systematic reviews (Online), no. 1, p. CD003967.

Withdrawn

Mahomed, K., 2007, WITHDRAWN: Iron supplementation in pregnancy: Cochrane database of systematic reviews (Online), no. 3, p. CD000117.

Mahomed, K., 2007, WITHDRAWN: Folate supplementation in pregnancy: Cochrane database of systematic reviews (Online), no. 3, p. CD000183.

Mahomed, K., 2007, WITHDRAWN: Iron and folate supplementation in pregnancy: Cochrane database of systematic reviews (Online), no. 3, p. CD001135.

Mahomed, K., 2007, WITHDRAWN: Prophylactic versus selective blood transfusion for sickle cell anaemia during pregnancy: Cochrane database of systematic reviews (Online), no. 3, p. CD000040.

Level II evidence

ACS

The following studies were excluded for reasons other than not meeting the PICO criteria:

Abstract only

Avanzas, P., R. rroyo-Espliguero, J. Quiles, A. Dominguez, and J. C. Kaski, 2010, C-reactive protein and hemoglobin levels predict future adverse cardiac events in patients with chronic stable angina pectoris: Circulation, v. 122, no. 2, p. e51.

Barrailler, S., V. Decourcelle, T. Guidez, S. Braun, J. J. Bauchart, J. L. Auffray, P. Asseman, and P. V. Ennezat, 2010, Prognostic value of anemia and haemoglobin changes in patients with acute coronary syndrome: Fundamental and Clinical Pharmacology, v. 24, p. 22.

Not in English

Reibis, R., J. Herbstleb, W. Kamke, R. Dissmann, K. Wegscheider, and H. Voller, 2007, Renal and cardiac functions as prognostic factors after revascularization for myocardial infarction: Deutsche Medizinische Wochenschrift, v. 132, no. 23, p. 1259–1263.

Duplicate data

Arant, C. B. et al., 2009, Multimarker approach predicts adverse cardiovascular events in women evaluated for suspected ischemia: Results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia syndrome Evaluation: Clinical Cardiology, v. 32, no. 5, p. 244–250.

Avanzas, P., R. rroyo-Espliguero, A. Dominguez-Rodriguez, and J. C. Kaski, 2010, C-reactive protein and hemoglobin levels predict future adverse cardiac events in patients with chronic stable angina pectoris: Atherosclerosis Supplements, v. 11, no. 2, p. 163.

Heart failure

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

Arques, S., B. Pieri, G. Biegle, E. Roux, R. Gelisse, and B. Jauffret, 2009, Comparative value of B-type natriuretic peptide and serum albumin concentration in the prediction of in-hospital mortality in elderly patients admitted for acute severe heart failure: Annales de Cardiologie et d'Angeiologie, v. 58, no. 5, p. 279–283.

Consuegra-Sanchez, L., J. Nunez, L. Facila, V. Bertomeu, R. Robles, and A. Llacer, 2006, Prognostic impact of anemia in acute heart failure: Revista de Investigacion Clinica, v. 58, no. 4, p. 279–284.

Dominguez Franco, A., J. P. Hernandez, M. P. Caravante, A. M. Garcia, M. J. Navarro, and E. D. T. Galvan, 2007, Long-term prognosis value of anemia in a non-selected population with heart failure: Medicina Clinica, v. 128, no. 10, p. 370–371.

Ferreira, S. A. M. P., R. Almeida, H. Guerrero, S. Lourenco-Ferreira, L. Fonseca, R. Rocha, F. Rocha-Goncalves, A. Ferreira, and P. Bettencourt, 2007, Prognosis of decompensated heart failure: Role of NT-proBNP: Revista Portuguesa de Cardiologia, v. 26, no. 5, p. 535–545.

Grigorian-Shamagian, L., A. Varela-Roman, P. Mazon-Ramos, M. Pedreira-Perez, P. Rigueiro-Veloso, and J. R. Gonzalez-Juanatey, 2005, Anemia as a new predictor of mortality in patients hospitalized with congestive heart failure: Medicina Clinica, v. 125, no. 17, p. 647–652+x.

Kamensky, G., R. Sidlo, J. Murin, J. Fabian, E. Goncalvesova, I. Riecansky, V. Bada, and A. Dukat, 2007, Incidence, predictors and prognostic relevance of worsening renal function in older patients with chronic heart failure in PROMISZ project: Kardiologia, v. 16, no. 3, p. 121–126.

Miklik, R., M. Felsoci, J. Parenica, D. Tomcikova, J. Jarkovsky, and J. Spinar, 2010, The prevalence of anemia and its impact on hospitalization mortality in patients with acute heart failure: Vnitrni Lekarstvi, v. 56, no. 5, p. 382–391.

Redondo-Bermejo, B., D. A. Pascual-Figal, J. A. Hurtado-Martinez, P. Penafiel-Verdu, D. Saura-Espin, I. P. Garrido-Bravo, J. Martinez-Sanchez, and M. Valdes-Chavarri, 2007, Influence of gender on the clinical characteristics and prognosis of patients hospitalized for heart failure: Revista Espanola de Cardiologia, v. 60, no. 11, p. 1135–1143.

Redondo-Bermejo, B., D. A. Pascual-Figal, J. A. Hurtado-Martinez, J. Montserrat-Coll, P. Penafiel-Verdu, F. Pastor-Perez, J. A. Giner-Caro, and M. Valdes-Chavarri, 2007, Clinical determinants and prognostic value of hemoglobin in hospitalized patients with systolic heart failure: Revista Espanola de Cardiologia, v. 60, no. 6, p. 597–606.

Zamora, E., J. Lupon, A. Urrutia, B. Gonzalez, D. Mas, T. Pascual, M. Domingo, and V. Valle, 2007, Does body mass index influence mortality in patients with heart failure?: Revista Espanola de Cardiologia, v. 60, no. 11, p. 1127–1134.

Abstract only

Despas, F. et al., 2010, Heart rate variability predicts short term mortality in acute heart failure patient: Fundamental and Clinical Pharmacology, v. 24, p. 23.

Duplicate data

Felker, G. M., J. D. Leimberger, R. M. Califf, M. S. Cuffe, B. M. Massie, J. Adams, M. Gheorghiade, and C. M. O'Connor, 2004, Risk stratification after hospitalization for decompensated heart failure: Journal of Cardiac Failure, v. 10, no. 6, p. 460–466.

No/insufficient adjustment for potential confounders

O'Meara, E. et al., 2006, Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure - Results of the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) program: Circulation, v. 113, no. 7, p. 986–994.

Elderly

No studies were excluded for reasons other than not meeting the PICO criteria.

Cancer

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

Borget, I., P. Tilleul, M. Baud, A. Granghaud, E. Iglesias, and C. Chouaid, 2007, A prospective study of quality of life and treatment of chemotherapy-induced anaemia in lung cancer: Revue des maladies respiratoires, v. 24, no. 1, p. 41–47.

Drings, P., and M. Wannenmacher, 2005, The effect of haemoglobin levels on prognosis and quality of life of patients with bronchial carcinoma: Deutsche Medizinische Wochenschrift, v. 130, no. 24, p. 1507–1511.

Glaus, A., and S. Muller, 2000, Haemoglobin and fatigue in cancer patients: Inseparable twins?: Schweizerische Medizinische Wochenschrift, v. 130, no. 13, p. 471–477.

Gullon, J., R. Fernandez, G. Rubinos, A. Medina, I. Suarez, and I. Gonzalez, 2001, Non-small cell bronchogenic carcinoma in advanced stages: prognostic value of weight loss and clinical implications: Archivos de bronconeumolog?a, v. 37, no. 11, p. 477–481.

Skladowski, K., A. Zajusz, J. Swiatnicka, M. Maciejewska, T. Krupska, S. Majewski, S. Szelc, J. Swiecki, and B. Maciejewski, 1996, Prognostic factors in radiotherapy of supraglottic cancer: Otolaryngologia polska.The Polish otolaryngology, v. 50, no. 6, p. 579–586.

Unal, D., and E. Yeni, 1999, Prognostic factors effecting overall, recurrence and progression free survival in bladder carcinoma: A multivariate analysis: Acta Urologica Italica, v. 13, no. 5–6, p. 215–220.

Abstract only

Buckstein, R., S. Alibhai, A. Lam, L. Zhang, M. Cheung, J. Callum, and R. Wells, 2009, Hemoglobin has the greatest impact on Quality Of Life (QOL) in MDS patients -a tertiary care cross sectional and longitudinal study: Leukemia Research, v. 33, p. S111-S112.

Egelmeer, A. G. T. M., J. M. De Jong, C. Dehing, L. Boersma, B. Kremer, and P. Lambin, 2009, Development of a nomogram for prediction of survival and local control in larynx carcinoma treated with radiotherapy alone: A cohort study based on 994 patients: European Journal of Cancer, Supplement, v. 7, no. 2–3, p. 473.

Harousseau, J. L., P. Fumoleau, W. Lange, and M. Welslau, 2005, Increasing hemoglobin levels with epoetin alfa in anemic hematologic cancer patients receiving chemotherapy correlates significantly with improved quality of life: Journal of Supportive Oncology, v. 3, no. 2 SUPPL. 1, p. 20–21.

Heng, D. Y. et al., 2009, Prognostic factors for overall survival (OS) in patients with metastatic renal cell carcinoma (RCC) treated with vascular endothelial growth factor (VEGF)-targeted agents: Results from a large multicenter study: Journal of Clinical Oncology, v. 27, no. 15, p. 5041.

Powell, E. D., T. Asmis, D. Jonker, D. Tu, C. Karapetis, M. Jeffery, and C. O'Callaghan, 2009, Comorbidity and overall survival (OS) in cetuximab-treated patients with advanced colorectal cancer (ACRC)-Results from NCIC CTG CO.17: A phase III trial of cetuximab versus best supportive care (BSC): Journal of Clinical Oncology, v. 27, no. 15, p. 4074.

Smith, M. R., R. J. Cook, and J. B. Nelson, 2010, Natural history of castration-resistant nonmetastatic prostate cancer: Secondary analyses of a multicenter randomized controlled trial: Journal of Clinical Oncology, v. 28, no. 15.

Duplicate data

Halabi, S., E. J. Small, P. W. Kantoff, M. W. Kattan, E. B. Kaplan, N. A. Dawson, E. G. Levine, B. A. Blumenstein, and N. J. Vogelzang, 2003, Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer: Journal of Clinical Oncology, v. 21, p. 1232–1237.

Verhoest, G., S. Zerrouki, M. Denis, N. Rioux-Leclercq, K. Bensalah, and J. J. Patard, 2009, Plasma and serumvegf prognostic factors in renal cancer: A prospective analysis in 367 patients: European Urology, Supplements, v. 8, no. 4, p. 155.

No/insufficient adjustment for potential confounding variables

Lind, M. et al., 2002, The level of haemoglobin in anaemic cancer patients correlates positively with quality of life: British Journal of Cancer, v. 86, no. 8, p. 1243–1249.

Included < 100 subjects

Brown, D. J. F., D. C. McMillan, and R. Milroy, 2005, The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer: Cancer, v. 103, no. 2, p. 377–382.

Renal

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

Vazquez, I., F. Valderrabano, I. Fort, R. Jofre, J. M. Lopez-Gomez, F. Moreno, and D. Sanz-Guajardo, 2004, Differences in health-related quality of life between male and female hemodialysis patients: Nefrolog?a : publicaci?n oficial de la Sociedad Espa?ola Nefrologia, v. 24, no. 2, p. 167–178.

No/insufficient adjustment for potential confounding variables

Locatelli, F. et al., 2004, Anaemia in haemodialysis patients of five European countries: Association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS): Nephrology Dialysis Transplantation, v. 19, no. 1, p. 121–132.

Pisoni, R. L. et al., 2004, Anemia management and outcomes from 12 countries in the dialysis outcomes and practice patterns study (DOPPS): American Journal of Kidney Diseases, v. 44, no. 1, p. 94–111.

Included < 100 subjects

Iliescu, E. A., H. Coo, M. H. McMurray, C. L. Meers, M. M. Quinn, M. A. Singer, and W. M. Hopman, 2003, Quality of sleep and health-related quality of life in haemodialysis patients: Nephrology Dialysis Transplantation, v. 18, no. 1, p. 126–132.

Wong, P. N., S. K. Mak, K. Y. Lo, G. M. W. Tong, Y. Wong, and A. K. M. Wong, 2003, Adverse prognostic indicators in continuous ambulatory peritoneal dialysis patients without obvious vascular or nutritional comorbidities: Peritoneal Dialysis International, v. 23, no. SUPPL. 2, p. S109-S115.

B2 Studies excluded from question 2

The literature search encompassed both the medical and critical care populations. As such, this list includes excluded citations relevant to both the medical and critical care populations.

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

The-Norwegian-Knowledge-Centre-for-the-Health-Services, 2005, Transfusion and alternative treatment in acute haemorrhage (Structured abstract): Oslo.: The Norwegian.Knowledge.Centre.for the Health Services, p. 119.

Not available/unable to be retrieved

Healthcare-Insurance-Board/, 2002, TACTICS: Transfusion Associated Complications or Transfusion Induced Complications - primary research (Brief record): Diemen.: Healthcare Insurance.Board/College voor Zorgverzekeringen..

University-HealthSystem-Consortium, 1997, Red blood cell transfusion guidelines (Structured abstract): Oak.Brook., Illinois.: University Healthsystem.Consortium., p. 138.

Superseded/duplicate data/withdrawn

Carson, J. L., S. Hill, P. Carless, P. Hebert, and D. Henry, 2002, Transfusion Triggers: A systematic review of the literature: Transfusion Medicine Reviews, v. 16, no. 3, p. 187–199.

Hill, S. R., P. A. Carless, D. A. Henry, J. L. Carson, P. C. Hebert, D. B. McClelland, and K. M. Henderson, 2002, Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion: Cochrane database of systematic reviews (Online), no. 2, p. CD002042.

Hill, S., P. A. Carless, D. A. Henry, J. L. Carson, P. C. Hebert-Paul, K. M. Henderson, and B. McClelland, 2000, Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion: Cochrane Database of Systematic Reviews.

Hirst, C., and W. C. Wang, 2002, Blood transfusion for preventing stroke in people with sickle cell disease: Hirst.Ceri., Wang.Winfred.C.Blood transfusion for preventing.stroke in people with sickle.cell disease.Cochrane Database of Systematic Reviews: Reviews 2002.Issue.1 John.Wiley.& Sons., Ltd.Chichester, UK DOI.: 10.1002./14651858.CD003146..

Mahomed, K., 2007, WITHDRAWN: Prophylactic versus selective blood transfusion for sickle cell anaemia during pregnancy: Cochrane database of systematic reviews (Online), no. 3, p. CD000040.

Riddington, C., and W. Wang, 2002, Blood transfusion for preventing stroke in people with sickle cell disease: Cochrane database of systematic reviews (Online), no. 1, p. CD003146.

Erratum/not relevant

Marik, P. E., and H. L. Corwin, 2008, Erratum: Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. (Critical Care Medicine (2008) 36 (2667–2674)): Critical Care Medicine, v. 36, no. 11, p. 3134.

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Abstract only

Abstract Presentations from the 2009 AABB Annual Meeting and TXPO: Transfusion, v. 49.

Fredrickson, 2010, Acute Physiological Effects of Red Blood Cell Transfusion in Preterm Infants Transfused Using Liberal or Restrictive Guidelines: Pediatric Academic Society, v. http://www.abstracts2view.com/pas/.

Colomo, A. et al., 2008, Transfusion strategies in patients with cirrhosis and acute gastrointestinal bleeding: Hepatology, v. 48, p. 413A.

Colomo, A. et al., 2009, Hemodynamic changes and transfusion strategies in cirrhotic patiens with acute variceal bleeding: Hepatology, v. 50, p. 403A.

Duplicate data

Kennedy, M. S., L. A. Kalish, K. Mohandas, T. Gernsheimer, and D. Townsend-McCall, 2002, The transfusion trigger and number of units transfused in patients with HIV: associations with disease stage and functional status: Transfusion, v. 42, no. 4, p. 456–461.

Includes < 100 subjects

Zygun, D. A., J. Nortje, P. J. Hutchinson, I. Timofeev, D. K. Menon, and A. K. Gupta, 2009, The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury: Critical Care Medicine, v. 37, no. 3, p. 1074–1078.

Level III evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Abstract only

Ahmed, A. H., M. Kojicic, G. Li, R. Kashyap, S. Thakur, V. Herasevich, and O. Gajic, 2009, Transfusion as a risk factor for hospital-acquired acute respiratory distress syndrome (ARDS) in Olmsted County Minnesota: Chest, v. 136, no. 4.

Andrzejewski, C., M. A. Popovsky, J. L. Provencher, T. C. Stec, and L. O'Hearn, 2009, Characteristics of patients with transfusion reactions associated with fluid challenges: Transfusion, v. 49, p. 196A-197A.

Badami, K., E. G. Merriman, and J. Dagger, 2009, FNHTR and infection/infammation may be related: Transfusion, v. 49, p. 195A.

Barrailler, S., V. Decourcelle, T. Guidez, S. Braun, J. J. Bauchart, J. L. Auffray, P. Asseman, and P. V. Ennezat, 2010, Prognostic value of anemia and haemoglobin changes in patients with acute coronary syndrome: Fundamental and Clinical Pharmacology, v. 24, p. 22.

Buckstein, R., S. Alibhai, A. Lam, L. Zhang, M. Cheung, J. Callum, and R. Wells, 2009, Hemoglobin has the greatest impact on Quality Of Life (QOL) in MDS patients -a tertiary care cross sectional and longitudinal study: Leukemia Research, v. 33, p. S111-S112.

Garcia Monje, M. J., M. Mourelo Farina, V. ler Fernandez, P. Fernandez Ugidos, R. Galeiras, T. Tabuyo Bello, D. Freire Moar, and P. Jimenez, 2009, Traumatic brain injury: Epidemiology, mortality risk factors and outcome: Intensive Care Medicine, v. 35, p. S73.

Goldberg, S. L., E. Chen, M. Corral, A. Guo, and M. Laouri, 2009, Influence of RBC transfusions on clinical outcomes among USA Medicare beneficiaries with newly diagnosed myelodysplastic syndromes: Leukemia Research, v. 33, p. S116.

Hearnshaw, S. A., T. Card, R. F. A. Logan, S. P. L. Travis, K. R. Palmer, and M. F. Murphy, 2009, Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding: Gut, v. 58, p. A33-A34.

Natukunda, B. M., H. Schonewille, and A. Brand, 2009, Red blood cell alloimmunization in sickle cell disease patients in Uganda: Transfusion, v. 49, p. 126A

Sada, F., M. Belegu, B. Zhubi, A. Geci, and M. Hashimi, 2009, Anemia, red blood cell transfusion and clinical outcomes in ICU patients: Transfusion Alternatives in Transfusion Medicine, v. 11, p. 30.

Not in English

Afonin, A. N., and N. A. Karpun, 2010, Acute transfusion-related lung injury in patients after cardiac surgery: Anesteziologiia i reanimatologiia, no. 2, p. 27–30.

Hernandez-Gutierrez, P., A. Grife-Coromina, and V. A. De la Garza-Estrada, 1997, Scales to evaluate mortality of patients with trauma and adult respiratory distress syndrome: Salud Publica de Mexico, v. 39, no. 3, p. 201–206.
Ref ID: 43991

Mukagatare, I., M. Monfort, J. de Marchin, and C. Gerard, 2010, The effect of leukocyte-reduction on the transfusion reactions to red blood cells concentrates: Transfusion Clinique et Biologique, v. 17, no. 1, p. 14–19.

No/insufficient adjustment for confounding variables

Bambha, K., W. R. Kim, R. Pedersen, J. P. Bida, W. K. Kremers, and P. S. Kamath, 2008, Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis: Gut, v. 57, no. 6, p. 814–820.

Bijlsma, T. S., P. J. C. M. Schure, L. P. H. Leenen, Y. Van Der Graaf, and C. Van Der Werken, 2005, The influence of blood transfusion on mortality in multiply injured patients: European Journal of Trauma, v. 31, no. 2, p. 154–157.

Ciesla, D. J. et al., 2004, Multiple organ dysfunction during resuscitation is not postinjury multiple organ failure: Archives of Surgery, v. 139, no. 6, p. 590–595.

Graves, T. A., W. G. Cioffi, J. Mason, W. F. McManus, and J. Pruitt, 1989, Relationship of transfusion and infection in a burn population: Journal of Trauma, v. 29, no. 7, p. 948–954.

Keller-Stanislawski, B., A. Reil, S. Gunay, and M. B. Funk, 2010, Frequency and severity of transfusion-related acute lung injury - German haemovigilance data (2006–2007): Vox Sanguinis, v. 98, no. 1, p. 70–77.

Previdi, J. K., C. G. Cayten, and D. W. Byrne, 1996, Early predictors of sepsis in the motor-vehicle crash trauma victim: Prehospital and disaster medicine : the official journal of the National Association of EMS Physicians and the World Association for Emergency and Disaster Medicine in association with the Acute Care Foundation, v. 11, no. 1,

Svennevig, J. L., B. Bugge-Asperheim, O. R. Geiran, J. Vaage, J. Pillgram-Larsen, N. B. Fjeld, and S. Birkeland, 1986, Prognostic factors in blunt chest trauma. Analysis of 652 cases: Annales Chirurgiae et Gynaecologiae, v. 75, no. 1, p. 8–14.

Taylor, R. W., L. Manganaro, J. O'Brien, S. J. Trottier, N. Parkar, and C. Veremakis, 2002, Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient: Critical Care Medicine, v. 30, no. 10, p. 2249–2254.

Includes < 100 subjects

Chen, B., Y. Xiao, G. Qian, L. Chen, Q. Zhong, and X. Wang, 2006, Risk factors associated with ARDS following cardiopulmonary bypass: Chinese Journal of Emergency Medicine, v. 15, no. 5, p. 429–432.

Cohen, A. R., M. B. Martin, J. H. Silber, H. C. Kim, K. Ohene-Frempong, and E. Schwartz, 1992, A modified transfusion program for prevention of stroke in sickle cell disease: Blood, v. 79, no. 7, p. 1657–1661.

Cornet, A. D., E. Zwart, S. D. K. Kingma, and A. B. J. Groeneveld, 2010, Pulmonary effects of red blood cell transfusion in critically ill, non-bleeding patients: Transfusion Medicine, v. 20, no. 4, p. 221–226.

de Montalembert, M., P. Beauvais, D. Bachir, F. Galacteros, and R. Girot, 1993, Cerebrovascular accidents in sickle cell disease. Risk factors and blood transfusion influence: European Journal of Pediatrics, v. 152, no. 3, p. 201–204.

Fenwick, J. C., M. Cameron, S. C. Naiman, L. P. Haley, J. J. Ronco, B. R. Wiggs, and M. G. Tweeddale, 1994, Blood transfusion as a cause of leucocytosis in critically ill patients: Lancet, v. 344, no. 8926, p. 855–856.

Fidone, C. et al., 2006, Clinical effects of different types of red cell concentrates in patients with thalassaemia: Blood Transfusion, v. 4, no. 4, p. 311–326.

Flores, J. M., P. I. Jimenez, M. D. Rincon, J. A. Marquez, H. Navarro, D. Arteta, and F. Murillo, 2001, Early risk factors for sepsis in patients with severe blunt trauma: Injury, v. 32, no. 1, p. 5–12.

Freedland, M., R. F. Wilson, J. S. Bender, and M. A. Levison, 1990, The management of flail chest injury: Factors affecting outcome: Journal of Trauma, v. 30, no. 12, p. 1460–1468.

Fuller, B., M. Gajera, C. Schorr, S. Zanotti, D. Gerber, R. P. Dellinger, and J. Parrillo, 2009, The impact of packed red blood cell transfusion on clinical outcomes in patients with septic shock treated with early goal directed therapy: Intensive Care Medicine, v. 35, p. S68.

George, M. E., D. E. Skarda, C. R. Watts, H. D. Pham, and G. J. Beilman, 2008, Aggressive red blood cell transfusion: No association with improved outcomes for victims of isolated traumatic brain injury: Neurocritical Care, v. 8, no. 3, p. 337–343.

Holguin, F., B. Ramadan, A. A. Gal, and J. Roman, 2008, Prognostic factors for hospital mortality and ICU admission in patients with ANCA-related pulmonary vasculitis: American Journal of the Medical Sciences, v. 336, no. 4, p. 321–326.

Jansen, A. J. G., M. A. A. Caljouw, W. C. J. Hop, D. J. Van Rhenen, and M. R. Schipperus, 2004, Feasibility of a restrictive red-cell transfusion policy for patients treated with intensive chemotherapy for acute myeloid leukaemia: Transfusion Medicine, v. 14, no. 1, p. 33–38.

Lee, S. W., T. Y. Lee, C. S. Chang, C. W. Ko, H. Z. Yeh, and S. S. Yang, 2010, Independent factors associated with early outcome in Chinese cirrhotic patients after cessation of initial esophageal variceal hemorrhage: Journal of Clinical Gastroenterology, v. 44, no. 6, p. e123-e127.

Mackinnon, S., A. K. Burnett, R. J. crawford, S. Cameron, B. G. S. Leask, and R. G. Sommerville, 1988, Seronegative blood products prevent primary cytomegalovirus infection after bone marrow transplantation: Journal of Clinical Pathology, v. 41, no. 9, p. 948–950.

Matsushima, K., A. Eastman, S. Shafi, A. Burris, T. Tyner, and H. Frankel, 2009, Transfusion increases infection without affecting neurologic outcome in spontaneous subarachnoid hemorrhage: Critical Care, v. 13, p. S41-S43.

Melchior, J. C., R. E. Poupon, and J. Verrier, 1987, Analysis of factors related to early death due to digestive hemorrhage in portal hypertension: Gastroenterologie Clinique et Biologique, v. 11, no. 5, p. 402–408.

Musau, P., 2006, Risk indicators of morbidity and mortality in abdominal injuries: East African medical journal, v. 83, no. 12, p. 644–650.

Schenk, J. F., B. Stephan, S. Morsdorf, K. Tilev, B. Krischek, E. Wenzel, L. Trumper, and U. T. Seyfert, 2000, Rational use of blood and blood components in hematology and oncology: Infusionstherapie und Transfusionsmedizin, v. 27, no. 4, p. 190–194.

Shalev, O., N. Manny, and R. Sharon, 1993, Posttransfusional hemolysis in recipients of glucose-6-phosphate dehydrogenase deficient erythrocytes: Vox Sanguinis, v. 64, no. 2, p. 94–98.

Slim, R., C. Yaghi, K. Honein, J. Bou Jaoude, S. El Khoury, and R. Sayegh, 2005, Factors predictive of clinical outcome in upper gastrointestinal bleeding: Journal Medical Libanais, v. 53, no. 3, p. 143–150.

Stoll, V. M., P. Medd, A. Peniket, P. Vyas, T. Littlewood, and C. Hatton, 2010, Analysis of factors affecting outcome in recipients of bone marrow transplantation for myelodysplasia; A single centre's experience over a nine year period: British Journal of Haematology, v. 149, p. 81–82.

Tan, F. L. S., Y. M. Tan, A. Y. F. Chung, P. C. Cheow, P. K. H. Chow, and L. L. Ooi, 2006, Factors affecting early mortality in spontaneous rupture of hepatocellular carcinoma: ANZ Journal of Surgery, v. 76, no. 6, p. 448–452.

Wood, J., and D. Pandit, 2009, Outcome of severe sepsis in the ICU is independent of haemoglobin levels: Critical Care, v. 13, p. S143.

Inconsistent results

Croce, M. A., E. A. Tolley, J. A. Claridge, and T. C. Fabian, 2005, Transfusions result in pulmonary morbidity and death after a moderate degree of injury: Journal of Trauma - Injury, Infection and Critical Care, v. 59, no. 1, p. 19–24.

Wrong intervention/comparator

Inoue, Y., Y. Wada, Y. Motohashi, and A. Koizumi, 2010, History of blood transfusion before 1990 is associated with increased risk for cancer mortality independently of liver disease: A prospective long-term follow-up study: Environmental Health and Preventive Medicine, v. 15, no. 3, p. 180–187.

Duplicate data

Sauaia, A., F. A. Moore, E. E. Moore, J. B. Haenel, R. A. Read, and D. C. Lezotte, 1994, Early predictors of post-injury multiple organ failure: Archives of Surgery, v. 129, p. 39–45.

B3 Studies excluded from question 3

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Protocol only

Albaramki J, Hodson EM, Craig JC (2009) Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database of Systematic Reviews (3).

No useable data

Dar Santos AE, Partovi N, Ford JAE, Yoshida EM (2007) Use of hematopoietic growth factors as adjuvant therapy for anaemia and neutropenia in the treatment of hepatitis C. Annals of Pharmacotherapy 41(2):268–75.

High versus low/low target haemoglobin

Clement FM, Klarenbach S, Tonelli M, Johnson JA, Manns BJ (2009) The impact of selecting a high haemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. Archives of Internal Medicine 169(12):1104–12.

Phrommintikul A, Haas SJ, Elsik M, Krum H (2007) Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 369(9559):381–388.

Strippoli GF, Navaneethan SD, Craig JC (2006) Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. Cochrane database of systematic reviews (4).

Strippoli GP, Craig JC, Manno C, Schena FP (2004) Hemoglobin targets for the anemia of chronic kidney disease: a meta-analysis of randomized, controlled trials. Journal of the American Society of Nephrology 15:3154–65.

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Non-validated functional orperformance status measure

Bertino G, Ardiri A, Boemi PM, Calvagno GS, Ruggeri M, Speranza A, Santonocito MM, Lerna D, Bruno CM, Valenti M, Boemi R, Naimo S, Neri S (2010) Epoetin alpha improves the response to antiviral treatment in HCV-related chronic hepatitis. European Journal of Clinical Pharmacology 66(10):1055–63.

High versus low/low target haemoglobin[1]

Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al (1998) The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. New England Journal of Medicine 339(9):584–90.

Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D et al (2006) Normalization of haemoglobin level in patients with chronic kidney disease and anemia. New England Journal of Medicine 355(20):2071–84.

Gouva C, Nikolopoulos P, Ioannidis JPA, Siamopoulos KC (2004) Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney International 66(2):753–60.

Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, et al (2000) Effect of haemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney International 58(3):1325.

Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG (2003) A randomized controlled trial of haemoglocin normalization with epoetin alfa in pre-dialysis and dialysis patients. Nephrology Dialysis Transplantation 18(2):353–61.

Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, Carlisle E, et al (2005) Canadian randomized trial of haemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. American Journal of Kidney Disease 46(5):799–811.

Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D (2005) Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. Journal of the American Society of Nephrology 16(7):2180–9.

Ritz E, Laville M, Bilous RW, O'Donoghue D, Scherhag A, Burger U, et al (2007) Target level for haemoglobin correction in patients with diabetes and CKD: primary results of the Anemia Correction in Diabetes (ACORD) Study. American Journal of Kidney Disease 49(2):194–207.

Roger SD, McMahon LP, Clarkson A, Disney A, Harris D, Hawley C, et al (2004) Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. Journal of the American Society of Nephrology 15(1):148–56.

Rossert J, Levin A, Roger SD, Horl WH, Fouqueray B, Gassmann-Mayer C, et al (2006) Effect of early correction of anemia on the progression of CKD. American Journal of Kidney Disease 47(5):738–50.

Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al (2006) Correction of anemia with epoetin alfa in chronic kidney disease. New England Journal of Medicine 355(20):2085–98.

[1] As defined by Tonelli M, Klarenbach S, Wiebe N, Shrive F, Hemmelgarn B, Manns B (2008) Erythropoesis stimulating agents for anemia of chronic kidney disease: systematic review and economic evaluation. [Technology report number 106]. Ottawa: Canadian Agency for Drugs and Technologies in Health.

B4 Studies excluded from question 4

The following studies were excluded for reasons other than not meeting the PICO criteria:

Level IV platelet studies with < 100 patients

Akkok, C. A., L. Brinch, G. F. Lauritzsen, B. G. Solheim, and J. Kjeldsen-Kragh, 2007, Clinical effect of buffy-coat vs. apheresis platelet concentrates in patients with severe thrombocytopenia after intensive chemotherapy: Vox Sanguinis, v. 93, no. 1, p. 42–48.

Anderson, N. A. et al., 1997, A prospective randomized study of three types of platelet concentrates in patients with haematological malignancy: Corrected platelet count increments and frequency of nonhaemolytic febrile transfusion reactions: Transfusion Medicine, v. 7, no. 1, p. 33–39.

Bishop, J. F. et al., 1988, Clinical factors influencing the efficacy of pooled platelet transfusions: Blood, v. 71, no. 2, p. 383–387.

Blumberg, N., J. M. Heal, and J. M. Rowe, 2004, A randomized trial of washed red blood cell and platelet transfusions in adult acute leukemia [ISRCTN76536440]: BMC Blood Disorders, v. 4.

Blundell, E. L. et al., 1996, A prospective, randomized study of the use of platelet concentrates irradiated with ultraviolet-B light in patients with hematologic malignancy: Transfusion, v. 36, no. 4, p. 296–302.

Bowden, R. A., S. J. Slichter, M. H. Sayers, M. Mori, M. J. Cays, and J. D. Meyers, 1991, Use of leukocyte-depleted platelets and cytomegalovirus-seronegative red blood cells for prevention of primary cytomegalovirus infection after marrow transplant: Blood, v. 78, no. 1, p. 246–250.

Callow, C. R., R. Swindell, W. Randall, and R. Chopra, 2002, The frequency of bleeding complications in patients with haematological malignancy following the introduction of a stringent prophylactic platelet transfusion policy: British Journal of Haematology, v. 118, no. 2, p. 677–682.

Chairulfatah, A., D. Setiabudi, R. Agoes, and R. Colebunders, 2003, Thrombocytopenia and platelet transfusions in dengue haemorrhagic fever and dengue shock syndrome: Dengue Bulletin, v. 27, p. 138–143.

Chambers, L. A., M. S. Kruskall, D. G. Pacini, and L. M. Donovan, 1990, Febrile reactions after platelet transfusion: The effect of single versus multiple donors: Transfusion, v. 30, no. 3, p. 219–221.

De Wildt-Eggen, J., S. Nauta, J. G. Schrijver, M. Van Marwijk Kooy, M. Bins, and H. C. Van Prooijen, 2000, Reactions and platelet increments after transfusion of platelet concentrates in plasma or an additive solution: A prospective, randomized study: Transfusion, v. 40, no. 4, p. 398–403.

Diedrich, B., M. Remberger, A. Shanwell, B. M. Svahn, and O. Ringden, 2005, A prospective randomized trial of a prophylactic platelet transfusion trigger of 10 null 109 per L versus 30

null 109 per L in allogeneic hematopoietic progenitor cell transplant recipients: Transfusion, v. 45, no. 7, p. 1064–1072.

Downey, D. M., B. Monson, K. L. Butler, J. Fortuna, J. M. Saxe, J. P. Dolan, R. J. Markert, and M. C. McCarthy, 2009, Does platelet administration affect mortality in elderly head-injured patients taking antiplatelet medications?: American Surgeon, v. 75, no. 11, p. 1100–1103.

Eernisse, J. G., and A. Brand, 1981, Prevention of platelet refractoriness due to HLA antibodies by administration of leukocyte-poor blood components: Experimental Hematology, v. 9, no. 1, p. 77–83.

Eichacker, P. Q., J. H. Shelhamer, M. Brenner, and J. E. Parrillo, 1990, The effects of heterologous platelet transfusion on pulmonary function during ARDS: Chest, v. 97, no. 4, p. 923–926.

Eriksson, L., A. Shanwell, H. Gulliksson, C. F. Hogman, L. Svensson, J. Kristensen, and B. Berg, 1993, Platelet concentrates in an additive solution prepared from pooled buffy coats. In vivo studies: Vox Sanguinis, v. 64, no. 3, p. 133–138.

Gil-Fernandez, J. J. et al., 1996, Clinical results of a stringent policy on prophylactic platelet transfusion: Non-randomized comparative analysis in 190 bone marrow transplant patients from a single institution: Bone Marrow Transplantation, v. 18, no. 5, p. 931–935.

Gmur, J., J. Burger, U. Schanz, J. Fehr, and A. Schaffner, 1991, Safety of stringent prophylactic platelet transfusion policy for patients with acute leukaemia: Lancet, v. 338, no. 8777, p. 1223–1226.

Gurkan, E., P. A. Patah, R. M. Saliba, C. A. Ramos, B. S. Anderson, R. Champlin, M. de Lima, and B. Lichtiger, 2007, Efficacy of prophylactic transfusions using single donor apheresis platelets versus pooled platelet concentrates in AML/MDS patients receiving allogeneic hematopoietic stem cell transplantation: Bone Marrow Transplantation, v. 40, no. 5, p. 461–464.

Heal, J. M., N. Kenmotsu, J. M. Rowe, and N. Blumberg, 1994, A possible survival advantage in adults with acute leukemia receiving ABO- identical platelet transfusions: American Journal of Hematology, v. 45, no. 2, p. 189–190.

Heal, J. M., J. M. Rowe, A. McMican, D. Masel, C. Finke, and N. Blumberg, 1993, The role of ABO matching in platelet transfusion: European Journal of Haematology, v. 50, no. 2, p. 110–117.

Heckman, K. D., G. J. Weiner, C. S. Davis, R. G. Strauss, M. P. Jones, and C. P. Burns, 1997, Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000/(mu)L versus 20,000/(mu)L: Journal of Clinical Oncology, v. 15, no. 3, p. 1143–1149.

Heddle, N. M. et al., 1999, A randomized controlled trial comparing plasma removal with white cell reduction to prevent reactions to platelets: Transfusion, v. 39, no. 3, p. 231–238.

Heddle, N. M. et al., 2002, A randomized controlled trial comparing the frequency of acute reactions to plasma-removed platelets and prestorage WBC-reduced platelets: Transfusion, v. 42, no. 5, p. 556–566.

Heddle, N. M., R. J. Cook, M. A. Blajchman, R. L. Barty, C. S. Sigouin, D. M. Boye, E. J. Nelson, and J. G. Kelton, 2005, Assessing the effectiveness of whole blood-derived platelets stored as a pool: A randomized block noninferiority trial: Transfusion, v. 45, no. 6, p. 896–903.

Ishida, A., M. Handa, M. Wakui, S. Okamoto, M. Kamakura, and Y. Ikeda, 1998, Clinical factors influencing posttransfusion platelet increment in patients undergoing hematopoietic progenitor cell transplantation - A prospective analysis: Transfusion, v. 38, no. 9, p. 839–847.

Kerkhoffs, J. L. H. et al., 2006, A multicenter randomized study of the efficacy of transfusions with platelets stored in platelet additive solution II versus plasma: Blood, v. 108, no. 9, p. 3210–3215.

Kerkhoffs, J. L. H., J. C. J. Eikenboom, L. M. G. Van De Watering, R. J. Van Wordragen-Vlaswinkel, P. W. Wijermans, and A. Brand, 2008, The clinical impact of platelet refractoriness: Correlation with bleeding and survival: Transfusion, v. 48, no. 9, p. 1959–1965.

Klumpp, T. R., J. H. Herman, J. P. Gaughan, R. R. Russo, R. A. Christman, S. L. Goldberg, S. J. Ackerman, G. C. Bleecker, and K. F. Mangan, 1999, Clinical consequences of alterations in platelet transfusion dose: A prospective, randomized, double-blind trial: Transfusion, v. 39, no. 7, p. 674–681.

Kurz, M., B. Eichelberger, H. Greinix, P. Hocker, P. Kahls, P. Knobl, W. R. Mayr, and S. Panzer, 1999, Platelet antibodies and fever: Their association in multitransfused patients with hemato-oncological diseases: Infusionstherapie und Transfusionsmedizin, v. 26, no. 1, p. 34–36.

Lee, E. J., and C. A. Schiffer, 1989, ABO compatibility can influence the results of platelet transfusion. Results of a randomized trial: Transfusion, v. 29, no. 5, p. 384–389.

Mangano, M. M., L. A. Chambers, and M. S. Kruskall, 1991, Limited efficacy of leukopoor platelets for prevention of febrile transfusion reactions: American Journal of Clinical Pathology, v. 95, no. 5, p. 733–738.

Muylle, L., E. Wouters, R. De Bock, and M. E. Peetermans, 1992, Reactions to platelet transfusion: the effect of the storage time of the concentrate: Transfusion medicine (Oxford, England), v. 2, no. 4, p. 289–293.

Nevo, S., A. K. Fuller, E. Hartley, M. E. Borinsky, and G. B. Vogelsang, 2007, Acute bleeding complications in patients after hematopoietic stem cell transplantation with prophylactic platelet transfusion triggers of 10 null 109 and 20 null 109 per L: Transfusion, v. 47, no. 5, p. 801–812.

Nevo, S., A. K. Fuller, M. L. Zahurak, E. Hartley, M. E. Borinsky, and G. B. Vogelsang, 2007, Profound thrombocytopenia and survival of hematopoietic stem cell transplant patients without clinically significant bleeding, using prophylactic platelet transfusion triggers of 10 null 109 or 20 null 10 9 per L: Transfusion, v. 47, no. 9, p. 1700–1709.

Norol, F., P. Bierling, F. Roudot-Thoraval, F. F. L. Coeur, C. Rieux, A. Lavaux, M. Kuentz, and N. Duedari, 1998, Platelet transfusion: A dose-response study: Blood, v. 92, no. 4, p. 1448–1453.

Pineda, A. et al., 2006, Pathogen inactivation of platelets with a photochemical treatment with amotosalen HCl and ultraviolet light: Process used in the SPRINT trial: Transfusion, v. 46, no. 4, p. 562–571.

Rebulla, P., G. Finazzi, F. Marangoni, G. Avvisati, L. Gugliotta, G. Tognoni, T. Barbui, F. Mandelli, and G. Sirchia, 1997, The threshold for prophylactic platelet transfusion in adults with acute myeloid leukemia: New England Journal of Medicine, v. 337, no. 26, p. 1870–1875.

Ronghe, M. D., A. B. M. Foot, J. M. Cornish, C. G. Steward, D. Carrington, N. Goulden, D. I. Marks, A. Oakhill, and D. H. Pamphilon, 2002, The impact of transfusion of leucodepleted platelet concentrates on cytomegalovirus disease after allogeneic stem cell transplantation: British Journal of Haematology, v. 118, no. 4, p. 1124–1127.

Saarinen, U. M., R. Kekomaki, M. A. Siimes, and G. Myllyla, 1990, Effective prophylaxis against platelet refractoriness in multitransfused patients by use of leukocyte-free blood components: Blood, v. 75, no. 2, p. 512–517.

Sintnicolaas, K., M. Van Marwijk Kooij, H. C. Van Prooijen, B. A. Van Dijk, W. L. J. Van Putten, F. H. J. Claas, V. M. J. Novotny, and A. Brand, 1995, Leukocyte depletion of random single-donor platelet transfusions does not prevent secondary human leukocyte antigen-alloimmunization and refractoriness: A randomized prospective study: Blood, v. 85, no. 3, p. 824–828.

Thomas, L. et al., 2009, Prospective observational study of low thresholds for platelet transfusion in adult dengue patients: Transfusion, v. 49, no. 7, p. 1400–1411.

Vo, T. D., J. Cowles, J. M. Heal, and N. Blumberg, 2001, Platelet washing to prevent recurrent febrile reactions to leucocyte-reduced transfusions: Transfusion Medicine, v. 11, no. 1, p. 45–47.

Wahlin, A., L. Eliasson, and H. Jonsson, 1990, Factors influencing the efficacy of platelet transfusions in acute leukemia: Leukemia and Lymphoma, v. 2, no. 5, p. 341–346.

Wali, J. P., A. Biswas, R. Handa, P. Aggarwal, N. Wig, and S. N. Dwivedi, 1999, Dengue haemorrhagic fever in adults: A prospective study of 110 cases: Tropical Doctor, v. 29, no. 1, p. 27–30.

Wandt, H. et al., 1998, Safety and cost effectiveness of a 10 x 109/L trigger for prophylactic platelet transfusions compared with the traditional 20 x 109/L trigger: A prospective comparative trial in 105 patients with acute myeloid leukemia: Blood, v. 91, no. 10, p. 3601–3606.

Zahur-ur-Rehman, A., and M. Alam, 2002, Platelet transfusion practice in a tertiary care hospital: Journal of the College of Physicians and Surgeons Pakistan, v. 12, no. 8, p. 485–487.

Zumberg, M. S., M. L. U. Del Rosario, C. F. Nejame, B. H. Pollock, L. Garzarella, K. J. Kao, R. Lottenberg, and J. R. Wingard, 2002, A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplat recipients: 10,000/(mu)L versus 20,000/(mu)L trigger: Biology of Blood and Marrow Transplantation, v. 8, no. 10, p. 569–576.

B5 Studies excluded from question 5

The following studies were excluded for reasons other than not meeting the PICO criteria:

Abstract only

Ali, M. A., S. Chaudhry, and F. T. Farooq, 2009, Acute gastrointestinal bleeding (GIB) in the setting of warfarin use and supratherapeutic inr (ST-INR): Frequency of significant endoscopic findings (EF) and independent predictors of GIB: Gastrointestinal Endoscopy, v. 69, no. 5, p. AB174.

Wandt, H. et al., 2009, Experience with a therapeutic platelet transfusion strategy in acute myeloid leukemia: Preliminary results of a randomized multicenter study after enrolment of 175 patients: Blood, v. 114, no. 22.

Not an RCT (platelets only)

Slichter, S. J., and L. A. Harker, 1978, Thrombocytopenia: mechanisms and management of defects in platelet production: Clinics in Haematology, v. 7, no. 3, p. 523–539.

Gmur, J., J. Burger, U. Schanz, J. Fehr, and A. Schaffner, 1991, Safety of stringent prophylactic platelet transfusion policy for patients with acute leukaemia: The Lancet, v. 338, no. 8777, p. 1223–1226.

Gil-Fernandez, J. J. et al., 1996, Clinical results of a stringent policy on prophylactic platelet transfusion: Non-randomized comparative analysis in 190 bone marrow transplant patients from a single institution: Bone Marrow Transplantation, v. 18, no. 5, p. 931–935.

Navarro, J. T., J. A. Hernandez, J. M. Ribera, J. M. Sancho, A. Oriol, M. Pujol, F. Milla, and E. Feliu, 1998, Prophylactic platelet transfusion threshold during therapy for adult acute myeloid leukemia: 10,000/(mu)l versus 20,000/(mu)l: Haematologica, v. 83, no. 11, p. 998–1000.

Sagmeister, M., L. Oec, and J. Gmur, 1999, A restrictive platelet transfusion policy allowing long-term support of outpatients with severe aplastic anemia: Blood, v. 93, no. 9, p. 3124–3126.

Lawrence, J. B., R. A. Yomtovian, T. Hammons, S. R. Masarik, V. Chongkolwatana, R. J. Creger, A. Manka, and H. M. Lazarus, 2001, Lowering the prophylactic platelet transfusion threshold: A prospective analysis: Leukemia and Lymphoma, v. 41, no. 1–2, p. 67–76.

Callow, C. R., R. Swindell, W. Randall, and R. Chopra, 2002, The frequency of bleeding complications in patients with haematological malignancy following the introduction of a stringent prophylactic platelet transfusion policy: British Journal of Haematology, v. 118, no. 2, p. 677–682.

Oka, S. et al., 2007, Evaluation of platelet transfusion thresholds in patients with acute myeloblastic leukemia receiving induction chemotherapy: Internal Medicine, v. 46, no. 19, p. 1669–1670.

Greeno, E., J. McCullough, and D. Weisdorf, 2007, Platelet utilization and the transfusion trigger: A prospective analysis: Transfusion, v. 47, no. 2, p. 201–205.

Nevo, S., A. K. Fuller, M. L. Zahurak, E. Hartley, M. E. Borinsky, and G. B. Vogelsang, 2007, Profound thrombocytopenia and survival of hematopoietic stem cell transplant patients without clinically significant bleeding, using prophylactic platelet transfusion triggers of 10 null 109 or 20 null 10 9 per L: Transfusion, v. 47, no. 9, p. 1700–1709.

Thomas, L. et al., 2009, Prospective observational study of low thresholds for platelet transfusion in adult dengue patients: Transfusion, v. 49, no. 7, p. 1400–1411.

Munasinghe, S. R., P. A. U. K. Senaviratne, D. Liyanapatabandi, and C. N. Seneviratne, 2010, Role of platelet transfusions and transfusion triggers in Dengue Hemorrhagic Fever: A single center experience from dengue epidemic region in Sri Lanka: Vox Sanguinis, v. 99, p. 429.

B6 Studies excluded from question 6

Level III evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

Germing U, Strupp C, Meckenstock G, Giagounidis A, Minning H, Aul C (1999) Clinical course, morphological findings and prognosis of CMML. MED KLIN 94(9):467–72.

No useable data

Agostoni P, Cerino M, Palermo P, Magini A, Bianchi M, Bussotti M, Fiorelli G, Cappellini MD (2005) Exercise capacity in patients with (beta)-thalassaemia intermedia. Br J Haematol 131(2):278–81.

Caocci G, Efficace F, Vignetti M, Mandelli F, Fazi P, Ledda A, La Nasa G (2009) Health-related quality of life of patients with myelodysplastic syndromes - A systematic review from 1980 to 2008. Haematologica 94:111.

Cario H, Stahnke K, Sander S, Kohne E (2000) Epidemiological situation and treatment of patients with thalassemia major in Germany: Results of the German multicenter (beta)-thalassemia study. Ann Hematol 79(1):7–12.

Castro-Malaspina H, Schaison G, Passe S (1984) Subacute and chronic myelomonocytic leukemia in children (juvenile CML). Clinical and hematologic observations and identification of prognostic factors. Cancer 54(4):675–86.

Coiffier B, Adeleine P, Gentilhomme O, Felman P, Treille-Ritouet D, Bryon PA (1987) Myelodysplastic syndromes. A multiparametric study of prognostic factors in 336 patients. Cancer 60(12):3029–32.

Correra A, Graziano JH, Seaman C, Piomelli S (1984) Inappropriately low red cell 2,3-diphosphoglycerate and p50 in transfused (beta)-thalassemia. Blood 63(4):803–6.

Dewulf G, Gouin I, Pautas E, Gaussem P, Chaibi P, Andreux JP, Siguret V (2004) Myelodisplasic syndromes diagnosed in a geriatric hospital: Morphological profile in 100 patients. Ann Biol Clin 62(2):197–202.

el Nawawy A, Massoud MN, El Bordiny M, Hegazy S (2002) Evaluation of serum soluble transferrin receptors and erythropoietin levels as indicators for erythropoietic activity among multi-transfused (beta)-thalassemic patients. J TROP PEDIATR 48(1):33–8.

Fenaux P, Jouet JP, Zandecki M (1987) Chronic and subacute myelomonocytic leukaemia in the adult: A report of 60 cases with special reference to prognostic factors. Br J Haematol 65(1):101–6.

Messa E, Cilloni D, Messa F, Arruga F, Roetto A, Saglio G (2008) Deferasirox treatment improved the hemoglobin level and decreased transfusion requirements in four patients with the myelodysplastic syndrome and primary myelofibrosis. ACTA HAEMATOL 120(2):70–4.

Necheles TF, Chung S, Sabbah R, Whitten D (1974) Intensive transfusion therapy in thalassemia major: an eight year follow up. Ann New York Acad Sci vol. 232:179–85.

Oguma S, Yoshida Y, Uchino H, Maekawa T, Womura T, Mizoguchi H (1995) Clinical charactertstics of Japanese patients with primary myelodysplastic syndromes: A co-operative study based on 838 cases. LEUK RES 19(3):219–25.

Oliva EN, Santini V, Antonella P, Liso V, Cilloni D, Terenzi A, Guglielmo P, Ghio R, Cortelezzi A, Semenzato G, Clissa C, Salvi F, Villani O, Spiriti MAA (2009) Quality of life in myelodysplastic syndromes and physicians' perception. Blood 114(22).

Schuler U (2007) Quality of life in patients with myelodysplastic syndromes. CANCER TREAT REV 33(SUPPL. 1):S59-S63.

Singh K, Pannu MS, Singh P, Singh J (2010) Effect of wheat grass tablets on the frequency of blood transfusions in Thalassemia Major. Indian J Pediatr 77(1):90–1.

Tantawy A, Moneim AAA, Ghareib M, Gelil SA (2009) Subclinical atherosclerosis in young B-thalassemia major patients. Haematologica 94:406.

Van Der Weide M, Sizoo W, Nauta JJP, Krefft J, Langenhuijsen MMAC (1988) Myelodysplastic syndromes: Analysis of clinical and prognostic features in 96 patients. Eur J Haematol 41(2):115–22.

Appendix C Literature search result

C1 Search results – Question 1

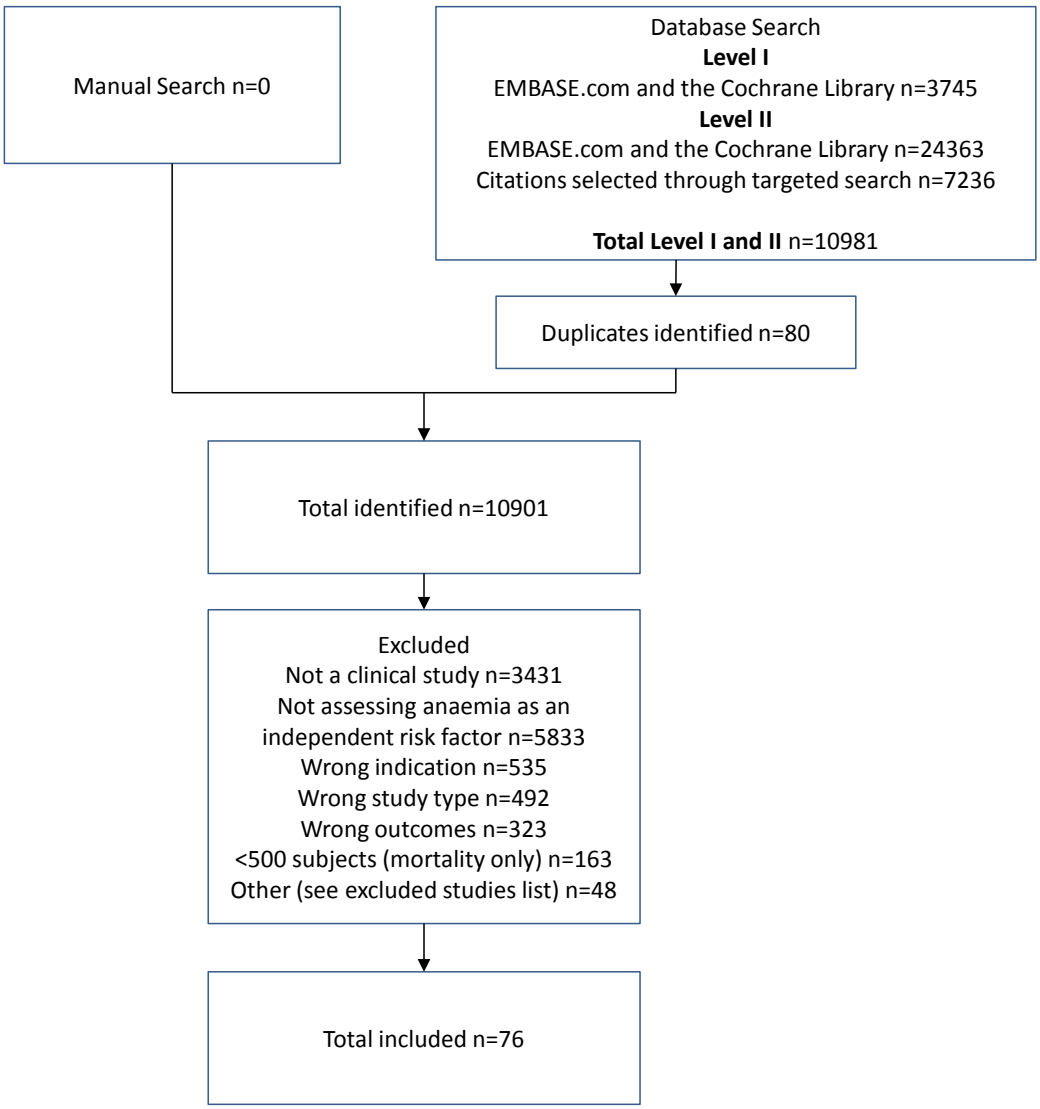

Figure C1 Search results – Question 1

C2 Search results – Question 2

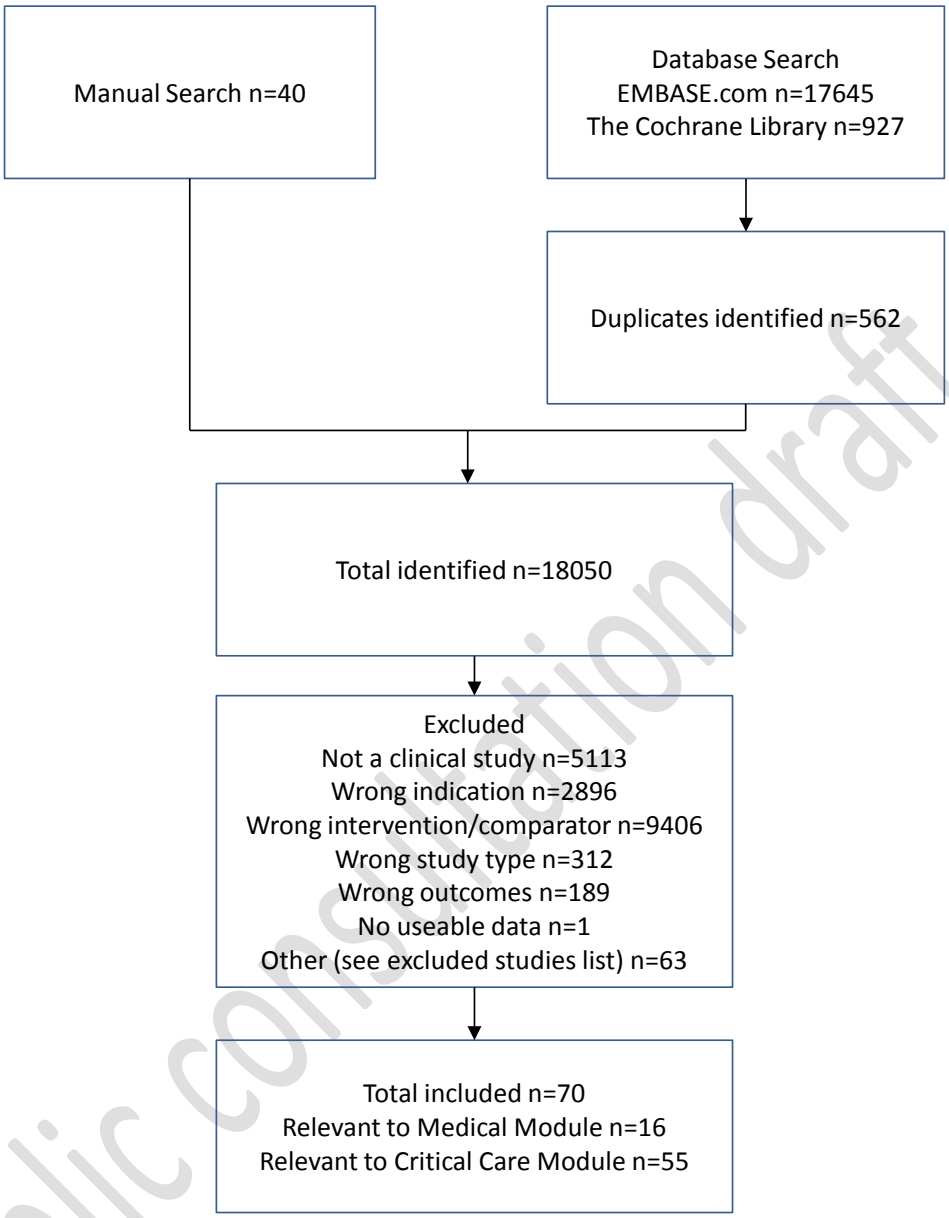

Figure C2 Search results – Question 2

C3 Search results – Question 3

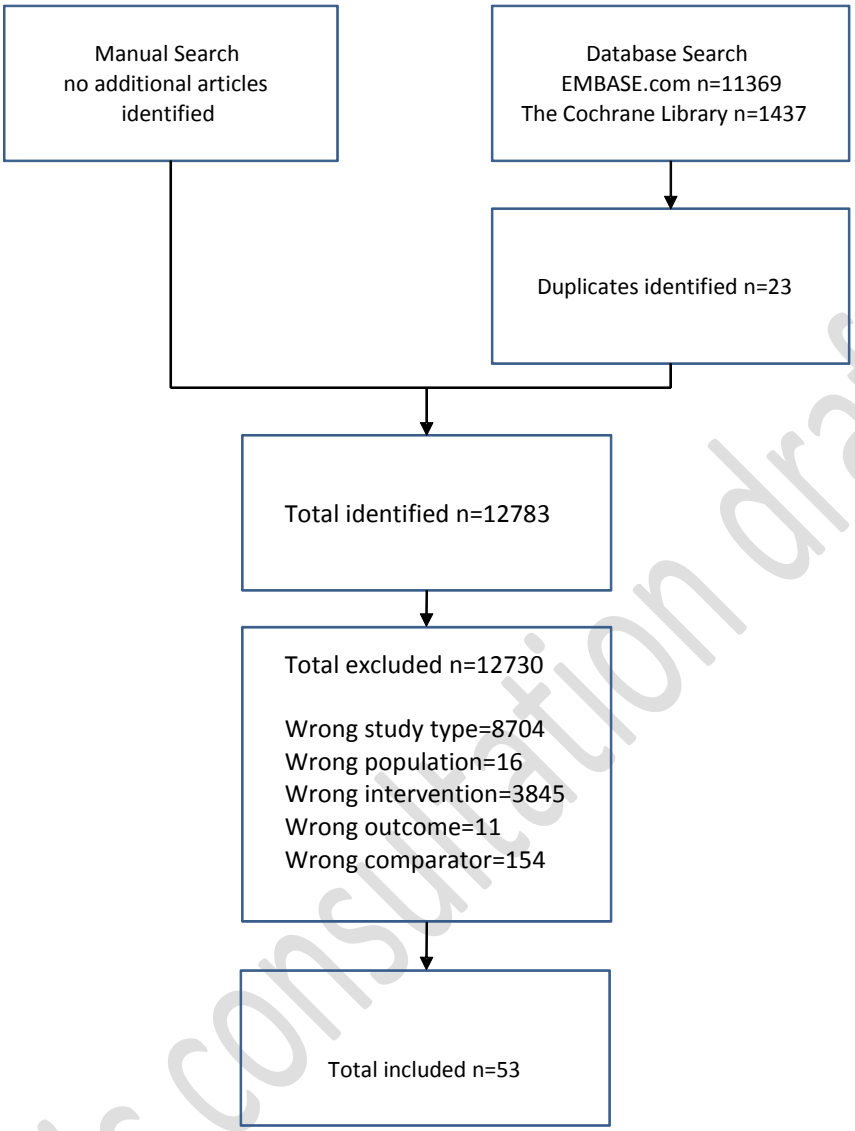

Figure C3 Search results – Question 3

C4 Search results – Question 4

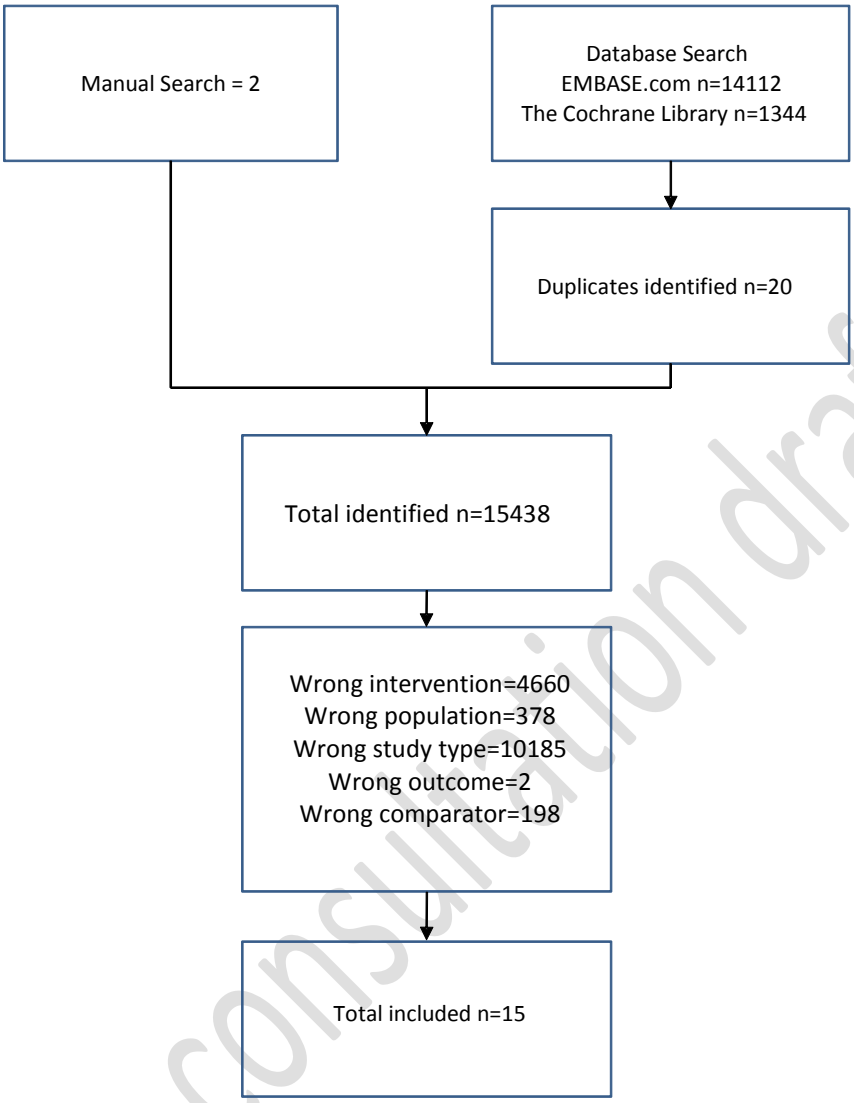

Figure C4 Search results – Question 4

C5 Search results – Question 5

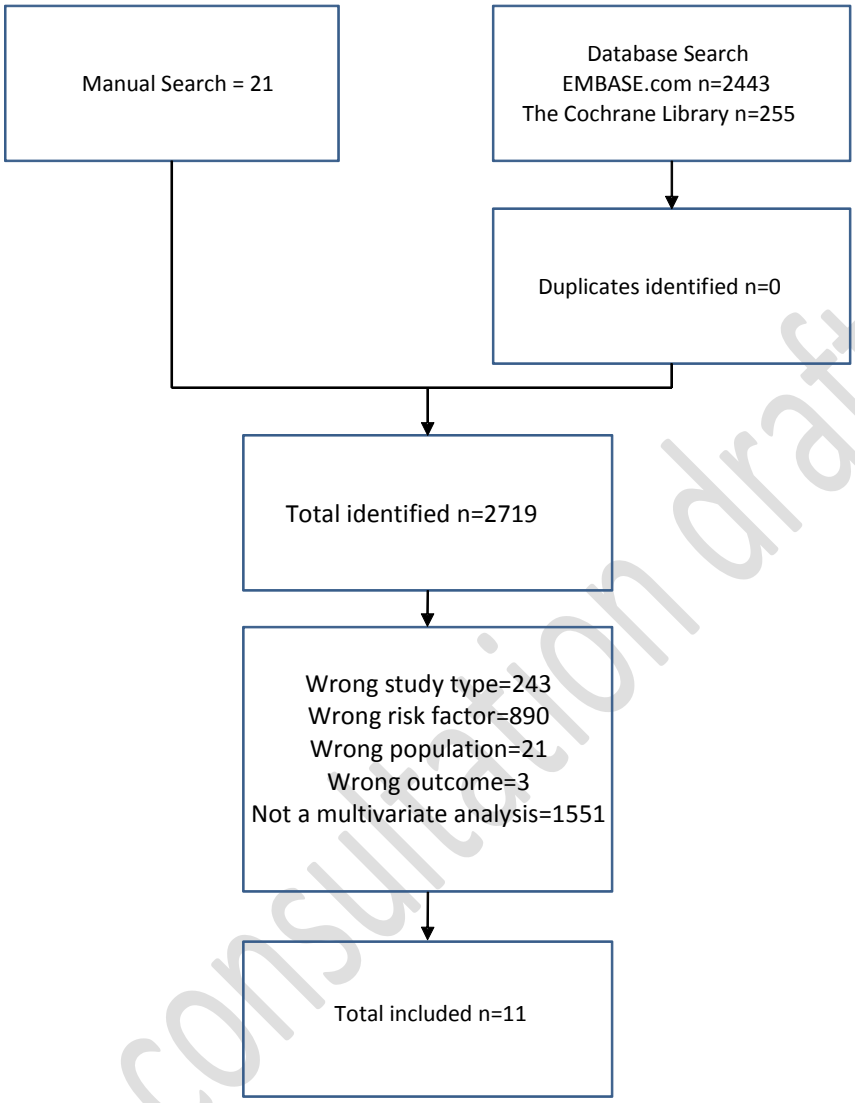

Figure C5 Search results – Question 5

C6 Search results – Question 6

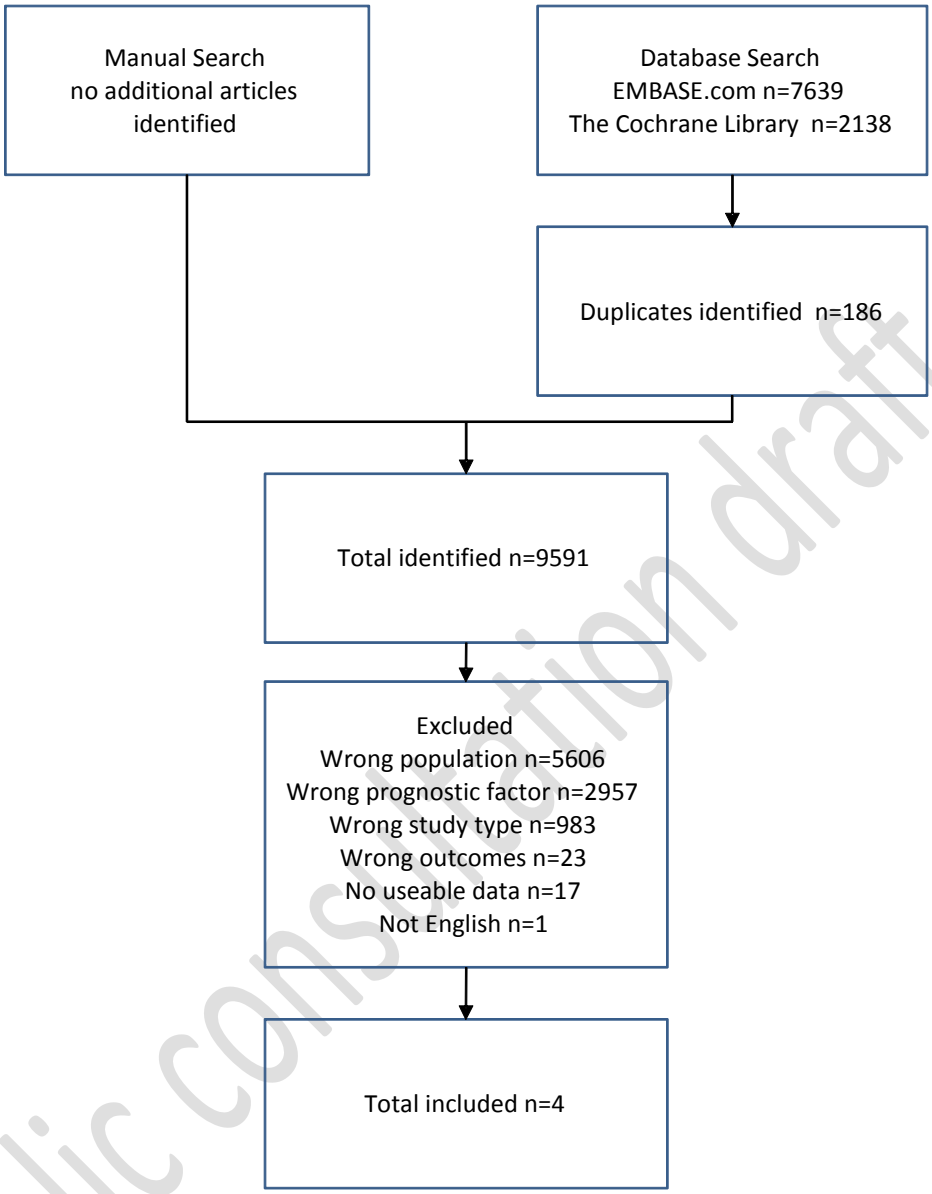

Figure C6 Search results – Question 6

Appendix D Evidence matrixes

Evidence matrixes are presented below for each intervention, subpopulation and outcome identified within each question of the Medical Module.

Where no evidence was found for a particular intervention, subpopulation or outcome, no evidence statement form has been presented and in the systematic review (Volume 1) the corresponding evidence statements are described as “unknown”. These evidence statements are not numbered or included in the main body of the guideline.

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

D1 Evidence – Question 1

Key question(s): In patients with ACS, is anaemia an independent risk factor for mortality?		Evidence Matrix: EM1.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 12 Level II studies of fair-good quality and 2 Level II studies of poor quality (Anker 2009-fair; Archbold 2006-fair; Aronson 2007-fair; Bassand 2010-fair; Burr 1992-poor; Cavusoglu 2006-fair; Giraldez 2009-good; Hasin 2009-fair; Keough-Ryan 2005-poor; Mahaffey 2008-good; Sabatine 2005-fair; Valeur 2009-fair). All studies included >500 subjects except Cavusoglu which was included as it assessed mortality/MI.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Results were generally consistent with the majority suggesting that anaemia/low Hb is an independent risk factor for mortality. Results that showed no association were usually because of a definition of mild anemia or a small reduction in Hb or the type of mortality measured (eg, cardiac mortality). In one study by Valeur et al (2006) anaemia or low haemoglobin as an independent risk factor for mortality appears to occur only in the subgroup of patients with heart failure, and not those with acute coronary syndrome without heart failure.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In studies that used the WHO definition of anaemia[a] or similar, the risk estimate of mortality associated with anemia/low haemoglobin was approximately 1.2 to 1.6 (2 studies). In studies which examined different haemoglobin cut-offs, low haemoglobin levels or large decreases in haemoglobin generally resulted in increased mortality. Other studies used various definitions of anemia and showed similar results. In analyses of Hb as a continuous variable, an increase/decrease in Hb was associated with a reduced/increased risk. Composite outcomes including mortality showed similar results.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included studies examined a wide variety of patients with ACS including those with MI, STEMI, NSTE-ACS and unstable angina. In addition, one study examined patients following MI who did or did not develop heart failure.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The included studies were conducted in a wide range of countries including Australia, Belgium, New Zealand, Denmark, Finland, Germany, Ireland, Norway, Sweden, UK, Israel, US, Canada, and other various locations. The results of these studies are likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

Only studies with > 500 subjects were included.
The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up. In particular, for the RCTs which were analysed as cohort studies it was sometimes difficult to tell whether all subjects included in the RCT had been included in the cohort analysis. In cases where this was noted, only a few compared the characteristics of those included and excluded from the analysis.
A number of studies noted limitations of their study, and a commonly noted limitation was the lack of
information on the cause of anaemia, and the possible impact this may have had on the results.
There were a wide range of different outcomes (eg, all-cause mortality, cardiovascular mortality, mortality + cardiovascular) and follow-up periods (ie, in-hospital to 12 years).

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
Evidence base	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
Consistency	B	Most studies consistent and inconsistency can be explained
Clinical impact	B	Substantial
Generalisability	A	Evidence directly generalisable to target population
Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES1.1 In patients with ACS, anaemia is independently associated with all-cause mortality.
ES1.2 In patients with ACS, the effect of anaemia on cardiovascular mortality is uncertain.

ACS, acute coronary syndrome; Hb, haemoglobin; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; RCT, randomised controlled trial; STEMI, ST-segment elevation myocardial infarction.
[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In patients with ACS, is anaemia an independent risk factor for cardiovascular outcomes?		Evidence Matrix: EM1.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level II study of fair quality (Sabatine 2005).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In patients with STEMI, Hb < 14 g/dL was associated with an increased risk of heart failure compared with a Hb ≥ 14 g/dL. In patients with NSTE-ACS, Hb < 11 g/dL was associated with an increased risk of MI and recurrent ischaemia compared with Hb 15–16 g/dL.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included study examined a wide variety of patients with ACS including those with STEMI and NSTE-ACS.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Only studies with > 500 subjects were included.
The main difference between studies rated as fair or good quality was the reporting of patient inclusion and follow-up. In particular, for the RCTs which were analysed as cohort studies it was sometimes difficult to tell whether all subjects included in the RCT had been included in the cohort analysis. In cases where this was noted, only a few compared the characteristics of those included and excluded from the analysis.
No evidence statement was developed for the heart failure outcome in patients with STEMI because while Hb level was significantly associated with heart failure, the patients were not anaemic (ie, Hb < 14 g/dL).

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	NA	Not applicable
3.	Clinical impact	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.3 In patients with NSTE-ACS, anaemia is independently associated with MI and recurrent ischaemia.

Hb, haemoglobin; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; RCT, randomised controlled trial; STEMI, ST-segment elevation myocardial infarction.

[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In patients with heart failure, is anaemia an independent risk factor for mortality?			Evidence Matrix: EM1.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes 13 Level II studies of fair-good quality and 1 Level II study of poor quality (Anand 2005-fair; Anker 2009-fair; Baggish 2007-fair; Ceresa 2005-poor; Felker 2003-good; Garty 2007-good; Hamaguchi 2009-fair; Ingle 2007-fair; Kalra 2003-fair; Komajda 2006-good; Maggioni 2005-good; Maraldi 2006-good; Poole-Wilson 2003-good; Young 2008-fair). All studies included > 500 subjects.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Results were generally consistent with the majority suggesting that anaemia/low Hb is an independent risk factor for mortality. Results that showed no association were usually because of a definition of mild anemia or a small reduction in Hb, the type of mortality measured (eg, cardiac mortality), the length of follow-up (eg, in hospital or a few months), the specific patient population assessed (eg, newly diagnosed heart failure) and in one study, gender (significant for females and not males).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
In studies which used the WHO definition of anaemia[a] or similar, the risk estimate of mortality associated with anemia/low haemoglobin was approximately 1.2 to 1.7 (7 studies). In one study which assessed mortality risk by gender, there was no increased risk associated with WHO-defined anaemia in men, but a 2-fold increased risk in women. Other studies used various definitions of anemia and showed similar results. In analyses of Hb as a continuous variable, an increase in Hb was associated with a reduced risk.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The included studies examined wide variety of patients with heart failure including chronic heart failure, acute heart failure, AMI with heart failure, those hospitalised due to heart failure, newly diagnosed heart failure and heart failure and left ventricular function < 50%.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The included studies were conducted in a wide range of countries including Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, the Netherlands, New Zealand, Norway, Portugal, Slovak Republic, Spain, Sweden, Switzerland , UK, US. The results of these studies are likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

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

Only studies with > 500 subjects were included.
The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up. In particular, for the RCTs which were analysed as cohort studies it was sometimes difficult to tell whether all subjects included in the RCT had been included in the cohort analysis. In cases where this was noted, only a few compared the characteristics of those included and excluded from the analysis.
A number of studies noted limitations of their study, and a commonly noted limitation was the lack of information on the cause of anaemia, and the possible impact this may have had on the results.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES1.4 In patients with heart failure, anaemia is independently associated with mortality.

Hb, haemoglobin.

[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In patients with heart failure, is anaemia an independent risk factor for functional/performance status?		Evidence Matrix: EM1.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one good quality Level II study (Adams 2009) which included > 500 subjects.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Statistically significant improvements in quality of life were seen for the KCCQ Functional, Symptom and Clinical subscales when data was analysed both categorically (MD 1.1, 1.5 and 0.9, respectively) and continuously. Statistically significant improvements in quality of life were seen for MLHFQ Physical subscale when analysed categorically (MD -0.4), and the Physical and Summary subscales when analysed continuously.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included study examined outpatients with heart failure who attended selected specialist heart failure clinics.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The included study was conducted in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Only studies with > 500 subjects were included.
The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up. In particular, for the RCTs which were analysed as cohort studies it was sometimes difficult to tell whether all subjects included in the RCT had been included in the cohort analysis. In cases where this was noted, only a few compared the characteristics of those included and excluded from the analysis.
A number of studies noted limitations of their study, and a commonly noted limitation was the lack of information on the cause of anaemia, and the possible impact this may have had on the results.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	NA	Not applicable
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.5 In patients with heart failure, anaemia may be independently associated with reduced functional or performance status and quality of life.

Hb, haemoglobin.

[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In elderly patients, is anaemia an independent risk factor for mortality?		Evidence Matrix: EM1.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 10 Level II studies of fair-good quality (Chavez 2004-fair; Denny 2006-fair; Dong 2008-fair; Endres 2009-good; Izaks 1999-fair; Patel 2007-fair; Patel 2009-good; Pennix 2007-fair; Riva 2009-good; Zakai 2005-fair). All studies included > 500 subjects overall.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Of the four studies which assessed WHO-defined anaemia[a] in an elderly population overall (without subgrouping), all consistently showed anaemia was an independent risk factor for mortality. Cases where anaemia was not found to be an independent risk factor were when mortality was measured from 5–10 years and when cardiovascular mortality was the outcome. Similar results were seen in three studies when different Hb levels were assessed, with lower Hb resulting in increased risk of mortality. Various subgroup analyses were undertaken including gender (four studies), race (three studies), anaemia subtype (three studies) and gender/race (one study) and race/type (one study). Results generally showed anemia/Hb was an independent risk factor but there were some inconsistencies in the gender results.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Of the four studies which assessed WHO-defined anaemia in an elderly population overall (without subgrouping), all showed anaemia was an independent risk factor for mortality with risk estimates ranging from 1.4 to 2.2. Of the three studies which assessed different definitions of anemia or different Hb levels, all showed low Hb was a significant predictor of Hb (risk estimate 1.3–2.0); the exception was when the Hb level was only slightly less than normal.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included studies examined community-dwelling subjects, generally aged ≥ 65 years. A number of studies included analyses by race, including Caucasian/white, African American/black and Mexican American populations. One study was specifically conducted in disabled women, the rest were in men and women.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The included studies were conducted in the US, Germany, the Netherlands and Italy. The results of these studies are likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Only studies with > 500 subjects overall were included. However, in some cases the number of subjects available for subgroup analyses was substantially below 500.
The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up. In particular, for the RCTs which were analysed as cohort studies it was sometimes difficult to tell whether all subjects included in the RCT had been included in the cohort analysis. In cases where this was noted, only a few compared the characteristics of those included and excluded from the analysis.
A number of studies noted limitations of their study, and a commonly noted limitation was the lack of information on the cause of anaemia, and the possible impact this may have had on the results. It should be noted that three studies assessed mortality risk by anaemia type/cause; one found that microcytic and normocytic anaemia were associated with increased risk while macrocytic anaemia was not, another found that anaemia associated with nutrient deficiency or chronic inflammation was associated with significantly increased risk but anaemia associated with kidney dysfunction, or when unexplained, was not, while the final study noted that anaemia of chronic disease with or without β-thalassemia was associated with increased risk.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.6 In a community-dwelling elderly population, anaemia is independently associated with mortality.

Hb, haemoglobin.

[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In elderly patients, is anaemia an independent risk factor for functional/performance status?		Evidence Matrix: EM1.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one good quality Level II study (Lucca 2008) which included > 500 subjects and one fair quality Level II study (Thein 2009) which included < 500 subjects.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies showed low haemoglobin was associated with worse disease-specific quality of life. The Thein study also suggested worse QoL using a number of the SF-36 subscales and worse function based on the IADL. Inconsistencies in general QoL could be due to different scales used (SF-12 vs SF-36) and that the reference Hb used in Thein was as the high end of normal (> 15 g/dL).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Lucca 2008 assessed outcomes using mild anaemia defined using the WHO criteria; 29.9% with mild anaemia has SF-12 Physical score < 40 compared with 19.5% without mild anaemia (p=0.0665). Significant difference seen for disease specific QoL (FACT-An Anaemia [P=0.0456] and Fatigue (P=0.0109). Disease specific QoL also significant in Thein study. In Thein study, low Hb was also significantly associated with a number of SF-36 subscales and IADL.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included studies examined elderly community-dwelling subjects.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The included studies were conducted in the US and Italy.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up. In particular, for the RCTs which were analysed as cohort studies it was sometimes difficult to tell whether all subjects included in the RCT had been included in the cohort analysis. In cases where this was noted, only a few compared the characteristics of those included and excluded from the analysis.
A number of studies noted limitations of their study, and a commonly noted limitation was the lack of information on the cause of anaemia, and the possible impact this may have had on the results.
Both studies were cross-sectional; however, they have been classified as Level II as this is the most appropriate study type to determine QoL/functional status associated with anaemia and because they used prospective collection of QoL/ functional data.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.7 In a community-dwelling elderly population, anaemia may be independently associated with reduced functional or performance status and quality of life.

Hb, haemoglobin.

[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In patients with cancer, is anaemia an independent risk factor for mortality?			Evidence Matrix: EM1.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes 7 Level II studies of fair-good quality and 4 Level II studies of poor quality (Armstrong 2010-good; Beer 2006-good; Cook 2006-fair; Halabi 2009-poor; Köhne 2002-poor; Laurie 2007-fair; Mandrekar 2006-poor; Négrier 2002-fair; Østerlind 1986-poor, Paesmans 1995-fair, Paesmans 2000-fair). All included studies examined >500 subjects. Eight studies with between 400–500 subjects were excluded.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Results were generally consistent with the majority suggesting that anaemia/low Hb is an independent risk factor for increased mortality/reduced survival. The majority of results that showed no association came from one study (Laurie 2007) in which a number of different measures of Hb were used (ie, nadir, % reduction, pre-PCI measurement). While this study included 523 subjects, for the categorical change analyses the number would have been substantially lower. Other non-significant findings came from a validation analysis including <500 subjects conducted by Mandrekar 2006 and from two studies by Paesmans (1995 and 2000).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
In the single study that used the WHO definition of anaemia[a] (for men only) there was a 30% reduction in post-progression survival (Armstrong 2010). In the remaining studies which examined different Hb levels or Hb as a continuous variable, the decreased survival risk ranged from approximately 9% to 51%.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The included studies examined a variety of cancer types including prostate cancer (4 studies), colorectal cancer (1 study), lung cancer (5 studies) and renal cancer (1 study).	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The included studies were conducted in a wide range of countries including the Europe, US, Argentina, Australia, Canada, France, Brazil, Germany, UK, New Zealand, Italy, Chile, Switzerland, Austria, Belgium, Peru, Sweden, Uruguay and Denmark. The results of these studies are likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

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

Only studies with > 500 subjects were included. Eight studies with between 400–500 subjects were excluded.
The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up. In particular, for the RCTs which were analysed as cohort studies it was sometimes difficult to tell whether all subjects included in the RCT had been included in the cohort analysis. In cases where this was noted, only a few compared the characteristics of those included and excluded from the analysis.
It was sometimes difficult to tell whether the significant association between anaemia/Hb resulted in decreased or increased survival as sometimes risk estimates were > 1 and sometimes they were < 1, indicating that while overall survival may have been the noted outcome, the analysis may have been conducted on time to death.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	C	Moderate
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES1.8 In patients with cancer, anaemia is independently associated with mortality.

Hb, haemoglobin.

[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In patients with cancer, is anaemia an independent risk factor for functional/performance status?			Evidence Matrix: EM1.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes two poor quality Level II cross-sectional studies (Nieboer 2005; Wisløff 2005) which included 426 and 745 subjects, respectively.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
The only outcome in common between the two studies was fatigue, measured using the SF-36 in the Nieboer study and the EORTC-QLQ-30 in the Wisløff study. The results for this outcome were consistent when measured prior to treatment and not consistent when measured post-treatment.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Both Nieboer and Wisløff showed that anaemia /low Hb was associated with fatigue prior to cancer therapy as examined fatigue as measured by the SF-36 and EORTC-QLQ-30 (OR 3.5; 95% CI 1.7, 7.1 (P=0.001) and p=0.041, respectively). An association following treatment was only seen in the Wisløff study (p=0.010). The only other QoL domain associated (or potentially associated with) low Hb in the Wisløff study was Global QoL score (P=0.041 for pre-treatment and P=0.052 for post-treatment).	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The included studies examined two populations of cancer patients; women with high-risk breast cancer and adults with multiple myeloma.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The included studies were conducted in the Netherlands, Denmark, Norway and Sweden.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

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

Both studies were cross-sectional; however, they have been classified as Level II as this is the most appropriate study type to determine QoL/functional status associated with anaemia and because they used prospective collection of QoL/ functional data.
The included studies were rated as poor because of a lack of information on the characteristics of subjects excluded from the analysis, and the potential for bias associated with a subjective outcome where the anaemia/haemoglobin status may be known.

EVIDENCE STATEMENT MATRIX

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

Component		Score	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	D	Slight/restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.9 In patients with cancer, the effect of anaemia on functional or performance status and quality of life is uncertain.

Hb, haemoglobin.

Key question(s): In patients with renal disease, is anaemia an independent risk factor for mortality?		Evidence Matrix: EM1.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
All-cause mortality: Includes seven Level II studies of fair quality; one in CKD patients (Astor 2006) and sex in dialysis patients (Avram 2003; Fort 2010; Portolés 2007; Robinson 2005; Stevens 2004; Yen 2010). All studies included > 500 subjects overall although subgroup analyses may have included < 500 subjects. Cardiovascular mortality: Includes two level II studies; one good quality (Leeder 2005) and one fair quality (Astor 2006). Both studies included > 500 subjects, including in subgroup analyses.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Results were generally consistent with the majority suggesting that anaemia/low Hb is an independent risk factor for mortality. There was some inconsistency between the results although this could often be explained by differences in Hb cut-offs used, methods of measuring CKD, different durations of dialysis, different Hb measurement timepoints and factors adjusted for.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
All-cause mortality: In patients with mild and moderate CKD, those with anaemia were at greater risk of mortality than those without anaemia (HR 1.62 vs 1.02 for mild and 3.49 vs 1.72 for moderate). In patients on dialysis, those with lowest Hb levels generally at increased risk of mortality. Results supported by continuous Hb analyses. One study suggested risk modification by diabetes (ie, greater risk in those without diabetes compared to those with). Cardiovascular mortality: In patients with mild and moderate CKD, those with anaemia were at greater risk of mortality than those without anaemia (HR 2.78 vs 1.36 for mild and 4.38 vs 2.67 for moderate). Also, lower Hb levels generally resulted in a greater risk of mortality ~1.5 to 2.3 times greater.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included studies examined a variety of patients with renal disease including those with chronic kidney disease and those on dialysis, both haemodialysis and peritoneal dialysis.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The included studies were conducted in Australia, the US, Spain, Canada and Taiwan. The settings included the community (for CKD patients) and hospital (for dialysis patients). The results of these studies are directly applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Only studies with > 500 subjects were included. The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up.
A two publications from the Dialysis Outcomes and Practice Patterns Study (DOPPS) were excluded where patients were using EPO but this was not accounted for in the study analysis (either by adjusting of measurement of Hb) (Locatelli 2004; Pisoni 2004).
Effect modification due to diabetes was shown in one included study, with CKD patients with anaemia diabetes not at greater risk of mortality and patients with anemia and no diabetes at significantly greater risk.
Adjustment for diabetes in the continuous Hb analysis showed a greater risk of mortality when adjusted for diabetes.
This evidence does not tell us to what extent all-cause mortality is driven by cardiovascular mortality.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population with some caveats
5.	Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES1.10 In patients with CKD (including dialysis patients), anaemia is independently associated with all-cause or cardiovascular mortality.

CKD, chronic kidney disease; EPO, erythropoiesis-stimulating agent; Hb, haemoglobin; HR, hazard ratio;

Key question(s): In patients with renal disease, is anaemia an independent risk factor for cardiovascular outcomes?		Evidence Matrix: EM1.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level II study of fair quality (Abramson 2003). This is for stroke only, there is no evidence for myocardial infarction.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Stroke: In patients with CKD (creatinine clearance < 60 mL/min) compared with patients without CKD the risk of stroke in patients with WHO-defined anaemia[a] is greater than the risk of stroke in patients without anaemia (HR 5.43 [p<0.01] vs HR 1.41 [p=0.1]). Ischaemic stroke: In patients with CKD (creatinine clearance < 60 mL/min) compared with patients without CKD the risk of stroke in patients with WHO-defined anaemia is greater than the risk of stroke in patients without anaemia (HR 10.34 [p=0.03] vs NR).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included study examined patients with CKD. It is unclear if these patients are on dialysis although it has been assumed they are not.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up. No studies were identified which assessed myocardial infarction as a sole outcome. A number of studies were identified which included myocardial infarction as a composite outcome (usually with cardiovascular mortality and hospitalisation) but these have been excluded from consideration here (Astor 2006, Jurkovitz 2003, Tanaka 2007).

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	B	Substantial
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.11 In adults with CKD, anaemia is independently associated with stroke.

CKD, chronic kidney disease; HR, hazard ratio; MI, myocardial infarction; US, United States of America; WHO, World Health Organisation[a] Hb < 13 g/dL for males and < 12 g/dL for females.

Key question(s): In patients with renal disease, is anaemia an independent risk factor for mortality?		Evidence Matrix: EM1.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two fair quality studies in patients with CKD (Finkelstein 2009; Perlman 2005) and four studies in dialysis patients, two fair quality (Platinga 2007; Merkus 1997) and two poor quality (Mollaoglu 2004; Turk 2004). Studies included from 140 to 1186 subjects. All included studies assessed QoL using the SF-36.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The results were generally consistent across the included studies although there was some variations within SF-36 domains. A lack of significance in some studies may be due to the small sample sizes.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In the dialysis study, higher Hb (≥ 11 g/dL vs < 11 g/dL) was an independent predictor of QoL for the following domains: physical component summary, mental component summary, physical functioning, role physical, social function, pain and mental health. Similar results were seen in the CKD patients although some domains differed. Results assessing Hb as a continuous variable were supportive of these results.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included studies were conducted in patients with CKD not on dialysis, and in patients on dialysis.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in the US, Canada, Turkey and the Netherlands. The results of these studies are likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The main difference between a study rated as fair or good quality was the reporting of patient inclusion and follow-up.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	C	Moderate
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.12 In adults with CKD (including dialysis patients), Hb concentration is independently associated with reduced quality of life.

CKD, chronic kidney disease; Hb, haemoglobin; QoL, quality of life; SF-36, short form 36 question general health survey; US, United States of America

Recommendation(s) for anaemia in a medical population

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE TABLE**
As this was a prognostic question, no recommendations were made.		

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

D2 Evidence – Question 2

Key question(s): In a medical population, what is the effect of restrictive versus liberal red blood cell transfusion on mortality?		Evidence Matrix: EM2.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One Level I study (Carless 2010; good quality) including data from up to 9 RCTs (N=2461). Based on the quality ratings in the Cochrane review, 2 studies were fair quality and 7 studies were poor quality.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There was no heterogeneity in any of the analyses with the exception of the analysis of 60-day mortality which included 2 RCTs and had pHet=0.19 and I^2=42%.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no significant difference in mortality between restrictive and liberal transfusion for any mortality outcome with the exception of in-hospital mortality where restrictive transfusion resulted in significantly less mortality compared with liberal transfusion (RR 0.78; 0.62, 0.98); P=0.031. The in-hospital mortality analysis included data from 9 RCTs; eight of these were critical care/surgical, while one small RCT (n=50) was in gastrointestinal haemorrhage.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted (in medical patients)
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results of this study are generalisable to a broad population, most notably those in critical care and undergoing surgery. Only two studies in medical populations (one of which was not eligible for this review) were included in the analyses.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in a wide range of countries and are likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

In the surgical and critical care setting, restrictive RBC transfusion reduces the risk of in-hospital mortality compared with liberal RBC transfusion.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
6. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
7. Consistency	B	Most studies consistent and inconsistency can be explained
8. Clinical impact	D	Slight/Restricted
9. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
10. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENTES2.1 In medical patients, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain.

RBC, red blood cell

Key question(s): In patients with ACS, what is the effect of red blood cell transfusion on mortality?			Evidence Matrix: EM2.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes six Level III-2 studies (Alexander 2008, *fair quality*; Rao 2004, *good quality*; Sabatine 2005, *fair quality*; Shishehbor 2009, *good quality*; Wu 2001, *fair quality*; Yang 2005, *poor quality*).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias: ES (1)(3)(4)	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias: ES (2)	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Four studies which assessed the association between RBC transfusion and mortality consistently show an increased risk. Four studies which assessed the association between RBC transfusion and mortality stratified by Hb/Hct showed slightly different results at low Hct levels: in two studies RBC in patients with low Hct resulted in decreased mortality while other studies showed no difference in mortality at low levels. There are a number of differences between the studies which may explain these differences.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
An increased mortality risk associated with RBC transfusion ranging from 1.5 to nearly 5.5 times was seen in four studies. When stratified by admission Hct, two studies showed decreased mortality associated with RBC transfusion at low Hct/Hb levels (OR 0.22 to 0.69 for Wu 2001 and OR 0.42 for Sabatine 2005). Wu showed increased mortality risk at high Hct levels (OR 1.38–1.46). When stratified by nadir Hct, there was no difference in risk at low levels and an increased mortality risk at higher levels (OR 168 and 292 for Rao 2004 and 2.89 and 3.47 for Alexander 2008).	A	Very large	
	B	Substantial: ES (1)	
	C	Moderate: ES (2)	
	D	Slight/Restricted: ES (3)	
	NA	No difference: ES (4)	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
There is evidence for patients with different types of ACS including acute MI, STEMI and NSTE-ACS.	A	Evidence directly generalisable to target population: ES (1)(2)(3)(4)	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Studies primarily conducted in the US and other locations including Australia.	A	Evidence directly applicable to Australian healthcare context: ES (1)(3)(4)	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats: ES (2)	
	D	Evidence not applicable to Australian healthcare context	

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

For the purpose of this review, only the four studies which stratified by Hb/Hct were considered when drafting the evidence statements. This is because stratifying by Hb/Hct resulted in differential results to those seen in the overall population.

While most included studies stratified by Hct, for the purpose of this review and guideline this has been converted to Hb concentration. There was a difference in results of the included studies depending on whether they stratified by *admission* Hct or *nadir* Hct which is reflected in the different evidence statements.

The Wu study was based on the analysis of Medicare claims data. This could potentially lead to potential population bias (ie, if no claim is made for the transfusion then it will not be identified in the study). As ES (2) was based primarily on the results of the Wu study, the rating for the evidence base was decreased to D and for applicability was decreased to C.

The evidence base for the final three evidence statements was considered too low to make an evidence-based recommendation. A recommendation was made for the first evidence statement due to the strength of the evidence for this group.

EVIDENCE STATEMENT MATRIX

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

Component		Rating (1)	Rating (2)	Rating (3)	Rating (4)	Description
1.	Evidence base	C	D	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	B	B	B	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	B	C	D	NA	Substantial
4.	Generalisability	A	A	A	A	Evidence directly generalisable to target population
5.	Applicability	A	C	A	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

(1) ES2.2 In ACS patients with a Hb concentration >100 g/L, RBC transfusion may be associated with a higher risk of mortality, proportional to Hb concentration.

(2) ES2.3 In ACS patients with an *admission* Hb concentration <100 g/L, RBC transfusion may be associated with a lower risk of mortality.

(3) ES2.4 In ACS patients with a *nadir* Hb concentration <80 g/L, RBC transfusion may be associated with a lower risk of mortality.

(4) ES2.5 In ACS patients with a *nadir* Hb concentration of 80–100 g/L, RBC transfusion is not associated with an altered mortality risk.

ACS, acute coronary syndrome; Hb, haemoglobin; RBC, red blood cell

Key question(s): In patients with ACS, what is the effect of red blood cell transfusion on thromboembolic events?		Evidence Matrix: EM2.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 studies (Shishehbor 2009; *fair quality*).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
30-day MI: HR 3.44 (P<0.001) 6-month MI: HR 2.69 (P<0.001) 1-year MI: NR (not significantly associated with MI)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in patients with STEMI only.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study conducted in various locations including Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Evidence only available for MI; no evidence for other thromboembolic events (eg, stroke, DVT/PE etc).

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	B	Substantial
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.6 In patients with ACS, RBC transfusion may be associated with an increased risk of recurrence (up to 6 months) of myocardial infarction.

ACS, acute coronary syndrome; RBC, red blood cell

Key question(s): In patients with heart failure, what is the effect of red blood cell transfusion on mortality?		Evidence Matrix: EM2.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 studies (Garty 2009; *fair quality*).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In-hospital mortality: OR 0.48 (0.21, 1.11); P=0.08 30-day mortality: OR 0.29 (0.13, 0.64); P=0.02 1-year mortality: HR 0.74 (0.50, 1.09); P=0.12 4-year mortality: HR 0.86 (0.64, 1.14); P=0.29	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in patients with acute decompensated heart failure.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study conducted in Israel.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	Underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.7 In patients with heart failure, the effect of RBC transfusion on the risk of mortality is uncertain.

RBC, red blood cell

Key question(s): In patients with cancer what is the effect of red blood cell transfusion on mortality?		Evidence Matrix: EM2.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 studies (Khorana 2008; *fair quality*).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In-hospital mortality: OR 1.34 (1.29, 1.36).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in a large number of patients with cancer (N=503,185). Included the following categories of cancer: pancreas, brain, other abdominal, ovary, renal, lung, stomach, non-Hodgkin lymphoma and multiple cancers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study conducted in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Despite the inclusion of data from a large cohort study (> 500,000 patients) a recommendation not made due to the fact that only associative data was available and the possibility of residual confounding due to the retrospective nature of the study.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	C	Moderate
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.8 In patients with cancer, RBC transfusion may be associated with an increased risk of in-hospital mortality.

RBC, red blood cell

Key question(s): In patients with cancer what is the effect of red blood cell transfusion on thromboembolic events?		Evidence Matrix: EM2.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 studies (Khorana 2008; *fair quality*).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
In-hospital ATE: OR 1.53 (1.46, 1.61); P<0.001 In-hospital VTE: OR 1.60 (1.53, 1.67); P<0.001	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in a large number of patients with cancer (N=503,185). Included the following categories of cancer: pancreas, brain, other abdominal, ovary, renal, lung, stomach, non-Hodgkin lymphoma and multiple cancers.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study conducted in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	C	Moderate
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.9 In patients with cancer, RBC transfusion may be associated with an increased risk of in-hospital venous and arterial thromboembolic events.

RBC, red blood cell

Key question(s): In patients with upper gastrointestinal blood loss, what is the effect of restrictive versus liberal red blood cell transfusion on mortality?		Evidence Matrix: EM2.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study (Blair 1986; *poor quality*).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Blair 1986 (RCT): mortality 0/26 (0%) in the restrictive transfusion group and 2/24 (8.3%) in the liberal transfusion group.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in patients with acute upper gastrointestinal bleeding.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study conducted in the UK. Substantial change in practice in past 25 years (paper was published 1986)	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Rebleeding was an outcome in the Blair (Level II) and Hearnshaw (Level III) studies. Rebleeding should be considered as an outcome in any future guidelines.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	Underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	D	Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.10 In patients with acute upper gastrointestinal blood loss, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain.

RBC, red blood cell

Key question(s): In patients with upper gastrointestinal blood loss, what is the effect of red blood cell transfusion on mortality?		Evidence Matrix: EM2.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 study (Hearnshaw 2010; *good quality*).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Hearnshaw 2010 showed no significant association between RBC transfusion and 30-day mortality in the overall population (OR 1.28; 0.94, 1.74) and subgroup analyses (OR 1.10 to 1.40) but the consistently high OR indicate there may be an association, but that the study is underpowered to show it.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	No difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The study was conducted in patients with acute upper gastrointestinal bleeding.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study conducted in the UK. Time to endoscopy is longer than it is at Australian sites.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Rebleeding was an outcome in the Blair (Level II) and Hearnshaw (Level III) studies. Rebleeding should be considered as an outcome in any future guidelines.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference/underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.11 In patients with acute upper gastrointestinal blood loss, the effect of RBC transfusion on mortality is uncertain.

RBC, red blood cell

Recommendation(s) for RBC transfusion in ACS patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In ACS patients with a Hb concentration >100 g/L, RBC transfusion is not recommended because of an association with increased mortality.	C	EM2.B

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Note that it will not be a change in recommended practice.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Clinical, pathology and resource requirements are likely to be reduced.		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
There is a persistent belief that patients with ACS have improved outcomes with higher Hb concentrations.		
What could help to facilitate implementation of the recommendation?		
Incorporation of education on this topic within the BloodSafe eLearning program. Note that many hospitals use this program to certify that training in transfusion has been provided which is required for accreditation purposes. Inclusion of a requirement to practice in accordance with Guidelines in the Australian Commission for Safety and Quality in Health Care's Blood and Blood Product Standard. Development of an exemplar a national prescription form. Development of an algorithm to assist decision making.		

D3 Evidence – Question 3

Key question(s): In anaemic patients with cancer, what is the effect of ESAs vs no ESAs on mortality?					Evidence Matrix: EM3.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*					
Level I evidence: Tonelli 2009 (good quality; 52 trials; N=12,006; cancer-related anaemia; ESA vs. no ESA) Level II evidence published after Tonelli 2009 literature review: 3 RCTs: Hernandez 2009 (fair; N=386; non-myeloid malignancy; DAR vs. placebo); Hoskin 2009 (poor; N=282; head and neck cancer; EPO vs. no EPO); Pronzato 2010 (fair; N=223; breast cancer; EPO vs. no EPO)	All	Non-CIA	CIA		
	A	A	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*					
Tonelli 2009 found a significant effect in all patients. Pronzato 2010 found no significant effect and Hoskin 2009 and Hernandez 2009 did not report a risk effect.	A	A	A	All studies consistent	
	B	B	B	Most studies consistent and inconsistency can be explained	
	C	C	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	D	D	Evidence is inconsistent	
	NA	NA	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*					
Update of Tonelli 2009: Meta-analysis of all data shows a significant increase in mortality with ESA treatment (RR 1.14; 95%CI: 1.02, 1.27).	A	A	A	Very large	
	B	B	B	Substantial	
	C	C	C	Moderate	
	D	D	D	Slight/Restricted	
	NA	NA	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*					
The results for overall mortality are generalisable to all adult patients with cancer-related anaemia.	A	A	A	Evidence directly generalisable to target population	
	B	B	B	Evidence directly generalisable to target population with some caveats	
	C	C	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*				
All-cause mortality: Tonelli 2009 reviewed 52 RCTs from multiple countries, including Australia. Additional studies by Hoskin 2009, Hernandez 2009 and Pronzato 2010 were conducted in Australia, New Zealand, the United Kingdom, North America and Europe.	A	A	A	Evidence directly applicable to Australian healthcare context
	B	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	All	Non-CIA	CIA	Description
1. Evidence base	B	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	A	A	A	All studies consistent
3. Clinical impact	B	B	D	All: Substantial; CIA: Slight/restricted
4. Generalisability	A	A	A	Evidence directly generalisable to target population
5. Applicability	A	A	A	Evidence directly applicable to Australian healthcare context

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.1 In anaemic adults with cancer, ESA therapy increases the risk of all-cause mortality; this effect appears to be greater in patients with a Hb concentration over 100 g/L.
ES3.2 In adult cancer patients with non-chemotherapy induced anaemia, ESA therapy increases the risk of all-cause mortality.
ES3.3 In adult cancer patients with chemotherapy-induced anaemia, the effect of ESA therapy on mortality is uncertain.

All, all anaemic cancer patients; CIA; patients with chemotherapy-induced anaemia; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin

Key question(s): In anaemic patients with cancer, what is the effect of ESAs vs no ESAs on transfusion incidence?		Evidence Matrix: EM3.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: : Tonelli 2009 (good quality; 52 trials; N=12,006; cancer-related anaemia; ESA vs. no ESA) Level II evidence published after Tonelli 2009 literature review: 4 RCTs: Christodoulou 2009 (poor; N=337; solid tumours; EPO vs. no EPO); Hernandez 2009 (fair; N=386; non-myeloid malignancy; DAR vs. placebo); Pronzato 2010 (fair; N=223; breast cancer; EPO vs. no EPO); Tsuboi 2009 (fair; N=117; lung cancer and lymphoma; EPO vs. placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Tonelli 2009, Christodoulou 2009 and Hernandez 2009 showed a significantly lower transfusion incidence with ESAs. Tsuboi 2009 and Pronzato 2009 found a non-significant trend to lower transfusion incidence with ESA treatment. The heterogeneity found is expected, given the diverse patient population	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Update of Tonelli 2009: Meta-analysis of all data shows a significant reduction in transfusion incidence with ESA treatment (RR 0.64; 95% CI: 0.56, 0.72).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results for transfusion incidence are generalisable to all adult patients with cancer-related anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Tonelli 2009 reviewed 52 RCTs from multiple countries, including Australia. Additional studies by Christodoulou 2009, Hernandez 2009, Tsuboi 2009 and Pronzato 2010 were conducted in Australia, New Zealand, Japan, North America and Europe.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
Note: the evidence statement forms for transfusion incidence and volume were consolidated into one evidence statement, using the ratings for transfusion incidence.		

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian healthcare context

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.4 In anaemic adults with cancer, ESA therapy reduces transfusion incidence and volume.

CI, confidence interval; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; RCT, randomised controlled trial; RR, relative risk

Key question(s): In anaemic patients with cancer, what is the effect of ESAs vs no ESAs on transfusion volume?		Evidence Matrix: EM3.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: : Tonelli 2009 (good quality; 52 trials; N=12,006; cancer-related anaemia; ESA vs. no ESA) Level II evidence published after Tonelli 2009 literature review: 1 RCT: Christodoulou 2009 (poor; N=337; solid tumours; EPO vs. no EPO	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Both studies report a significant reduction in transfusion volume with ESAs.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Tonelli 2009: Meta-analysis of all data shows a significant reduction in transfusion volume with ESA treatment (WMD –0.80 units; 95%CI: –0.99, –0.61).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results for transfusion volume are generalisable to all adult patients with cancer-related anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Tonelli 2009 reviewed 52 RCTs from multiple countries, including Australia. Christodoulou 2009 was performed in Greece.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Note: the evidence statement forms for transfusion incidence and volume were consolidated into one evidence statement, using the ratings for transfusion incidence.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	A	All studies consistent
3.	Clinical impact	C	Moderate
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.4 In anaemic adults with cancer, ESA therapy reduces transfusion incidence and volume.

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; NA, not applicable; RCT, randomised controlled trial; SR, systematic review; WMD, weighted mean difference

Key question(s): In anaemic patients with cancer, what is the effect of ESAs vs no ESAs on thromboembolic events?		Evidence Matrix: EM3.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: Bohlius 2006 (good quality; 12 trials; N=1738; cancer-related anaemia; EPO vs. no EPO) Level II evidence published after Tonelli 2009 literature review: 8 RCTs identified by Tonelli 2009 (N=2138; cancer-related anaemia; ESAs vs. no ESAs);); Hernandez 2009 (fair; N=386; non-myeloid malignancy; Hoskin 2009 (poor; N=282; head and neck cancer; EPO vs. no EPO); Pronzato 2010 (fair; N=223; breast cancer; EPO vs. no EPO); Tsuboi 2009 (fair; N=117; lung cancer and lymphoma; EPO vs. placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Bohlius 2006, the additional studies from Tonelli 2009, Hoskin 2009 and Tsuboi 2009 all report a higher incidence in subjects treated with ESAs. This effect is significant in the additional studies form Tonelli 2009.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Update of Bohlius 2006: Meta-analysis of all data shows a significant increase in the risk of thromboembolic events with ESA treatment (RR 1.73; 95%CI: 1.29, 2.31).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results for thromboembolic events are generalisable to all adult patients with cancer-related anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Bohlius 2006 and Tonelli 2009 reviewed RCTs from multiple countries, including Australia. Additional studies by Hernandez 2009, Hoskin 2009, Tsuboi 2009 and Pronzato 2010 were conducted in Australia, New Zealand, Japan, North America, the United Kingdom and Europe.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	A	All studies consistent
3.	Clinical impact	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.5 In anaemic adults with cancer, ESA therapy increases the risk of thromboembolic events.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

Key question(s): In anaemic patients with cancer, what is the effect of ESAs vs no ESAs on functional and performance status?		Evidence Matrix: EM3.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: : Tonelli 2009 (good quality; 52 trials; N=12,006; cancer-related anaemia; ESA vs. no ESA) Level II evidence published after Tonelli 2009 literature review: 3 RCTs: Hoskin 2009 (poor; N=282; head and neck cancer; EPO vs. no EPO); Pronzato 2010 (fair; N=223; breast cancer; EPO vs. no EPO); Tsuboi 2009 (fair; N=117; lung cancer and lymphoma; EPO vs. placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Tonelli 2009 reported significant effects on FACT-Anaemia general and subscale scores and FACT-Fatigue subscale score, but not on FACT-Anaemia total score. Pronzato 2010 reported significant effects on all FACT-Anaemia scores. Hoskin 2009 reported no significant effect on all FACT-Anaemia scores. Tsuboi reported a significant effect on FACT-Fatigue score only in one patient subgroup.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Update of Tonelli 2009: Meta-analysis of all data shows a significant favourable effect on FACT total score with ESA therapy (WMD 4.25; 95% CI: 2.85, 5.65).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results for functional and performance status are generalisable to all adult patients with cancer-related anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Tonelli 2009 reviewed 52 RCTs from multiple countries, including Australia. Additional studies by Hoskin 2009, Tsuboi 2009 and Pronzato 2010 were conducted in the United Kingdom, Japan and Europe.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.6 In anaemic adults with cancer, ESA therapy may improve functional and performance status; however, the magnitude of this effect appears slight.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; FACT, functional assessment of cancer therapy; NA, not applicable

Key question(s): In anaemic patients with cancer, what is the effect of IV iron vs no IV iron on mortality?			Evidence Matrix: EM3.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level II evidence: 4 RCTs: Auerbach 2010 (good quality; N=238; DAR plus IV iron vs DAR with oral or no iron); Bastit 2008 (fair quality; N=396; DAR plus IV iron vs DAR with oral or no iron); Hedanus 2007 (poor quality N=67; EPO plus IV iron vs EPO alone); Pedrazzoli 2008 (fair quality; N=149; DAR plus IV iron vs DAR alone)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
None of the studies found a significant difference between treatment arms in mortality. There was moderate heterogeneity[a] (P=0.23; I^2=31%).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Results of meta-analysis: RR 0.93; 95% CI 0.49, 1.77; no difference	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results are generalisable to anaemic patients with cancer	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Auerbach 2010 was multicentre (USA and Europe); Bastit 2008 was multicentre (Europe); Hedanus 2008 was conducted in Sweden; Pedrazzoli 2008 was conducted in Italy.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
The studies were not powered to detect a difference in mortality, and follow-up duration was short.		
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base	B	One level II study with a low risk of bias, two level II studies with a moderate risk of bias, and one level II study with a high risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
DRAFT EVIDENCE STATEMENT *Based on the body of evidence above.*		
ES3.7 In anaemic adults with cancer receiving ESAs, the effect of IV iron versus oral or no iron on short-term mortality is uncertain.		

CI, confidence interval; DAR, darbepoetin; ESA, erythropoiesis-stimulating agent; EPO, erythropoietin; IV, intravenous; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with cancer, what is the effect of IV iron vs no IV iron on transfusion?			Evidence Matrix: EM3.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	ESA ± iron	IV vs oral iron	
Level II evidence: 4 RCTs: Auerbach 2010 (good quality; N=238; DAR plus IV iron vs DAR with oral or no iron); Bastit 2008 (fair quality; N=396; DAR plus IV iron vs DAR with oral or no iron); Dangsuwan 2010 (fair quality; N=44; IV vs oral iron); Pedrazzoli 2008 (fair quality; N=149; DAR plus IV iron vs DAR alone)	A	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Bastit et al (2008) and Dangsuwan et al (2010) found that patients treated with IV iron had a significantly lower incidence of RBC transfusion and a significantly lower median RBC transfusion volume compared with patients who did not receive IV iron. Pedrazzoli et al (2008) found no significant difference in transfusion incidence between DAR and IV iron compared with DAR alone. The treatment arms had a similar incidence of RBC transfusion in Auerbach et al (2010) (P=NR).	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
Auerbach 2010: KM percentage mean (95% CI) RBC transfusion incidence, %: 28 (20, 37) vs 30 (23, 39) Bastit 2008: KM proportion of patients receiving an RBC transfusion, %: 16 vs 25; P=0.038 Dangsuwan 2010: Incidence of RBC transfusion in consecutive cycle of chemotherapy: 22.7% vs 63.6%; P<0.05; favours IV iron Median (range) volume of RBCs transfused, units: 0 (0 to 2) vs 1 (0 to 2); P=0.01; favours IV iron Pedrazzoli 2008: Incidence of RBC transfusion: 2.7% vs 6.6%; RR 0.42 (0.08	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results are generalisable to anaemic patients with cancer	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Auerbach 2010 was multicentre (USA and Europe); Bastit 2008 was multicentre (Europe); Dangsuwan 2010 was conducted in Thailand; Pedrazzoli 2008 was conducted in Italy.	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		ESA ± iron	IV vs oral iron	Description
1.	Evidence base	B	C	One level II study with a low risk of bias, three level II studies with a moderate risk of bias
2.	Consistency	B	NA	Most studies consistent and inconsistency can be explained
3.	Clinical impact	C	B	Moderate
4.	Generalisability	B	A	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	C	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.8 In adults with cancer-related anaemia receiving ESAs, IV iron may reduce the incidence of RBC transfusion.

ES3.9 In anaemic patients with gynaecological cancer receiving chemotherapy, IV iron may reduce the incidence and volume of RBC transfusion.

CHF, chronic heart failure; CI, confidence interval; ESA, erythropoiesis stimulating agent; IV, intravenous; KM, Kaplan-Meier; NA, not applicable; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review manager.

Key question(s): In anaemic patients with cancer, what is the effect of IV iron vs no IV iron on thromboembolic events?		Evidence Matrix: EM3.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 3 RCTs: Auerbach 2010 (good quality; N=238; DAR plus IV iron vs DAR with oral or no iron); Bastit 2008 (fair quality; N=396; DAR plus IV iron vs DAR with oral or no iron); Pedrazzoli 2008 (fair quality; N=149; DAR plus IV iron vs DAR alone)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
All the studies were consistent in finding no difference. There was no significant heterogeneity[a] for overall thromboembolic events (P=0.82; I^2=0%), and moderate heterogeneity[a] for MI (P=0.21; I^2=36%).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Thromboembolic events (meta-analysis): RR 0.95; 95% CI: 0.54, 1.65; no difference MI (meta-analysis): RR 0.41; 95% CI 0.10, 1.64; no difference Stroke (Auerbach 2010): RR 3.10 (0.13, 75.38); no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to anaemic patients with cancer	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Auerbach 2010 was multicentre (USA and Europe); Bastit 2008 was multicentre (Europe); Pedrazzoli 2008 was conducted in Italy.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies were not powered to detect a significant difference in thromboembolic events.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One level II study with a low risk of bias, two level II studies with a moderate risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.10 In adults with chemotherapy-induced anaemia receiving ESAs, the effect of IV iron versus oral or no iron on the incidence of thromboembolic events is uncertain.

CI, confidence interval; DAR, darbepoetin; ESA, erythropoiesis-stimulating agent; IV, intravenous; MI, myocardial infarction; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with cancer, what is the effect of IV iron vs no IV iron on functional/performance status?			Evidence Matrix: EM3.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	ESA ± iron	IV vs oral	
Level II evidence: 2 RCTs: Bastit 2008 (fair quality; N=396; DAR plus IV iron vs DAR with oral or no iron); Dangsuwan 2010 (fair quality; N=44; IV vs oral iron)	A	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
All the studies were consistent in finding no significant difference	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
Bastit 2008 Mean (95% CI) adjusted change in FACT-Fatigue score from baseline at follow-up: 2.40 (0.84, 3.95) vs 2.17 (0.65, 3.69); no difference KM proportion (95% CI) of patients with a clinically meaningful increase in FACT-Fatigue **score (≥3 points), %:** 76 (67, 84) vs 67 (56, 78); no difference Dangsuwan 2010 Median (range) change in FACT-anaemia score from	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results are generalisable to anaemic patients with cancer	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Bastit 2008 was multicentre (Europe); Dangsuwan 2010 was conducted in Thailand	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		ESA ± iron	IV vs oral iron	Description
1.	Evidence base	C	C	Two level II studies with a moderate risk of bias
2.	Consistency	NA	NA	Not applicable
3.	Clinical impact	NA	NA	Not applicable/no difference/underpowered
4.	Generalisability	B	A	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.11 In adults with non-myeloid malignancies and chemotherapy-induced anaemia receiving ESAs, IV iron versus oral or no iron appears to have no effect on functional or performance status.

ES3.12 In anaemic patients with gynaecological cancer receiving chemotherapy, the effect of IV iron versus oral iron on functional or performance status is uncertain.

CI, confidence interval; DAR, darbepoetin; ESA, erythropoiesis-stimulating agent; IV, intravenous; FACT, Functional Assessment of Cancer Therapy; KM, Kaplan-Meier; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

[b] Calculated for the purpose of this systematic review using Review manager.

Key question(s): In anaemic patients with CHF, what is the effect of ESAs vs no ESAs on mortality?			Evidence Matrix: EM3.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence: 2 SRs: Ngo 2010 (good quality; 10 trials [3 good, 4 fair, 3 poor]; N=764; ESA vs no ESA); Desai 2010 (good quality; 9 trials [4 good, 3 fair, 2 poor]; N=2039; ESA vs no ESA)[a] No Level II evidence published subsequently	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Ngo 2010 found that ESAs significantly reduced mortality, Desai 2010 found no significant difference between treatment arms. The Desai study includes the large Pfeffer study, which was conducted in patients with HF who also had CKD and diabetes. There was no significant heterogeneity[b] in either the Ngo 2010 (P=0.67; I^2=0.0) or the Desai 2010 meta-analyses (P=0.21; I^2=NR).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
Ngo 2010 ESA vs no ESA (N=764): 5.9% vs 10.4%; RR 0.61; 95% CI 0.37, 0.99; favours ESA Desai 2010 ESA vs no ESA (N=2039): 21.9% vs 23.2%; RR 1.03; 95% CI 0.89, 1.21 EPO vs no EPO (N=81): 6.7% vs 8.3%; RR 0.70; 95% CI 0.28, 1.79 DAR vs no DAR (N=1988): 22.4% vs 23.8%; RR 0.82; 95% CI 0.48, 1.42	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results are generalisable to adults with CHF.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	
	NA	Not applicable/no difference/underpowered	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
All the studies were conducted in UK (Cleland 2005), USA (Ghali 2008, Mancini 2003), Greece (Kourea 2008, Parissis 2008, Parissis 2009), Italy (Palazzuoli 2006, Palazzuoli 2007), and multicentre (Ponikowski 2007, van Veldhuisen 2007). Pfeffer 2009 was conducted at 623 sites in 24 countries, including Australia.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

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

Note: when large Pfeffer paper included, no significant difference.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	A	Two level two studies with low risk of bias
2.	Consistency	D	Evidence is inconsistent
3.	Clinical impact	D	Slight/restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	A	Evidence directly applicable to Australian healthcare context

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.13 In anaemic patients with CHF, the effect of ESAs on mortality is uncertain.

CI, confidence interval; CHF, chronic heart failure; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; Hg, haemoglobin; NA, not applicable; RCT, randomised controlled trial; RR, relative risk; SR, systematic review

[a] Desai et al (2010) included a subpopulation (N=1347) of CHF patients from the Pfeffer et al (2009) trial, which randomised 4044 patients with type 2 diabetes mellitus, chronic kidney disease, and anaemia (Hg ≤ 110 g/L) to treatment with DAR or placebo. Furthermore, two studies not discussed in Desai et al (2010) (Palazzuoli et al [2006] and the unpublished results from Kourea et al [2008]) were included in the Ngo et al (2010) meta-analysis for mortality. Silverberg et al (2001) was included in the Ngo et al (2010) meta-analysis, but was excluded from Desai et al (2010) due to concerns regarding the lack of blinding, lack of placebo control, and potential confounding by concomitant administration of IV iron to ESA-administered patients. Desai et al (2010) identified one RCT (Parissis et al [2009]) that was published after the literature search conducted for Ngo et al (2010).

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet > 0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with CHF, what is the effect of ESAs vs no ESAs on blood transfusion?		Evidence Matrix: EM3.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: 1 pooled analysis: Klapholz 2009 (poor quality; 3 trials [all good]; N=514; DAR vs no DAR)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NR	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
DAR vs no DAR (incidence of RBC transfusion): N=514; 6.4% vs 9.5%; P=NR	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The studies conducted in adults with CHF, but most of these patients not candidates for transfusion. The definition of anaemia in the included studies does not match the Australian setting.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in USA and Europe.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The study appears to have combined unpublished data from three separate RCTs, without using appropriate methodology.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	D	One pooled analysis of level II studies with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	D	Slight/restricted
4.	Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.14 In anaemic patients with CHF, the effect of ESAs on transfusion requirements is uncertain.

CHF, chronic heart failure; DAR, darbepoetin; ESA, erythropoietin stimulating agent; NA, not applicable; NR, not reported; RBC, red blood cell

Key question(s): In anaemic patients with CHF, what is the effect of ESAs vs no ESAs on thromboembolic events?		Evidence Matrix: EM3.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence Stroke: Ngo 2010 (good quality; 8 trials [3 good, 3 fair, 1 poor]; N=700; ESA vs no ESA) MI: Ngo 2010 (good quality; 9 trials [3 good, 4 fair, 2 poor]; N=732; ESA vs no ESA) Thromboembolic events[a]: Ngo 2010 (good quality; 9 trials [3 good, 4 fair, 2 poor]; N=741; ESA vs no ESA)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Stroke: All the RCTs agreed in direction and found no significant difference between treatment arms. There was no significant heterogeneity[b] (P=0.86; I^2=0.0%). MI: All of the studies except one agreed in direction and none of the studies found a significant difference between treatment arms. There was no significant heterogeneity[b] (P=0.94; I^2=0.0%). Thromboembolic events[a]: Incidence was similar between treatment arms for all of the included RCTs. There was no significant heterogeneity[b] (P=0.59; I^2=0.0%).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Stroke: Ngo 2010 (N=700; 1.8% vs 1.3%; RR 1.57; 95% CI 0.52, 4.70); no significant difference MI: Ngo 2010 (N=732; 2.2% vs 3.7%; RR 0.69; 95% CI 0.31, 1.55); no significant difference Thromboembolic events[a]: Ngo 2010 (N=741; 1.0% vs 1.8%; RR 0.65; 95% CI 0.22, 1.88); no significant difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The definition of anaemia in some of the included studies does not match the Australian setting. The patients in these studies would not be eligible for transfusion.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
All the studies were conducted in UK (Cleland 2005), USA (Ghali 2008, Mancini 2003), Greece (Kourea 2008, Parissis 2008, Parissis 2009), Italy (Palazzuoli 2006, Palazzuoli 2007), and multicentre (Ponikowski 2007, van Veldhuisen 2007). Pfeffer 2009 was conducted at 623 sites in 24 countries including Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies were not powered to detect a significant difference in thromboembolic events. Pfeffer study – different patient group

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	A	One level I study with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.15 In anaemic patients with CHF, the effect of ESAs on the incidence of thromboembolic events is uncertain.

CHF, chronic heart failure; CI, confidence interval; DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoietin stimulating agent; MI, myocardial infarction; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

[a] Includes any thromboembolic event other than MI or stroke.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with CHF, what is the effect of ESAs vs no ESAs on functional/performance status?		Evidence Matrix: EM3.M
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence 6MWT distance: Ngo 2010 (good quality; 4 trials [1 good, 2 fair, 1 poor]; N=261; ESA vs no ESA) NYHA functional class: Ngo 2010 (good quality; 8 trials [2 good, 4 fair, 2 poor]; N=657; ESA vs no ESA)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
6MWT: Although all the studies agreed in direction, there was substantial heterogeneity[a] ($P=0.02$; $I^2=70\%$). NYHA functional class: All the studies agreed in direction, but some found no significant difference between treatment arms. There was substantial heterogeneity[a] ($P<0.001$; $I^2=95\%$).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
6MWT: Ngo 2010 (N=261; MD 69.33; 95% CI 16.99, 121.67; Favours ESA) NYHA functional class: Ngo 2010 (N=657; MD -0.73; 95% CI -1.11, -0.36; Favours ESA)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The definition of anaemia in some of the included studies does not match the Australian setting. The patients in these studies would not be eligible for transfusion.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in USA and Europe.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Although the evidence base was rated 'A', no recommendation was made because the evidence for mortality, transfusion requirements and thromboembolic events was uncertain, and function/performance was a secondary outcome.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	A	One Level I study with a low risk of bias
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	C	Moderate
4.	Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.16 In anaemic patients with CHF, ESAs may improve functional or performance status compared with no ESAs.

6MWT, 6-minute walk test; CI, confidence interval; CHF, chronic heart failure; ESA, erythropoiesis stimulating agent; MD, mean difference; NA, not applicable; NYHA, New York Heart Association

[a] 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 if I^2>50%.

Key question(s): In CHF patients with iron deficiency, what is the effect of IV iron vs no IV iron on mortality?			Evidence Matrix: EM3.N
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level II evidence: 2 RCTs: Anker 2009 (good quality; N=459; IV iron vs placebo); Okonko 2008 (poor quality; N=18; IV iron vs standard care)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Neither of the studies found a significant difference between treatment arms in mortality. There was no significant heterogeneity[a] (P=0.58; I^2=0%).	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
Overall mortality (meta-analysis): RR 0.73; 95% CI 0.22, 2.41; no difference Mortality due to cardiovascular causes (Anker 2009): RR 1.62; 95% CI 0.08, 34.66; no difference	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results are generalisable to CHF patients with iron deficiency.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible	

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Anker 2009 was multicentre (11 countries), Okonko 2008 was conducted in UK and Poland.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies were not powered to detect a difference in mortality.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One level II study with a low risk of bias and one level II study with a high risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.17 In CHF patients with iron deficiency, the effect of IV iron on mortality is uncertain.

CHF, chronic heart failure; CI, confidence interval; IV, intravenous; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In CHF patients with iron deficiency, what is the effect of IV iron vs no IV iron on functional/performance status?			Evidence Matrix: EM3.O
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level II evidence: 2 RCTs: Anker 2009 (good quality; N=459; IV iron vs placebo); Okonko 2008 (poor quality; N=18; IV iron vs standard care)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
Both RCTs found there was a greater improvement in NYHA for IV iron compared with control. Other outcomes NA.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
Anker 2009 Patients with an improvement in Self-Reported Patient Global Assessment at follow-up: 73.7% vs 52.9%; OR 2.49; 95% CI: 1.66, 3.74; favours IV iron Patients with an improvement in NYHA functional class at follow-up: OR 2.40; 95% CI: 1.55, 3.71; favours IV iron 6MWT: mean (SD) treatment effect 35 (8); P<0.001; favours IV iron EQ-5D: mean (SD) treatment effect 7 (2); P<0.001; favours IV iron Kansas City Cardiomyopathy Questionnaire: mean (SD) treatment effect 7 (2); P<0.001; favours IV iron Okonko 2008 NYHA functional status: mean (95% CI) treatment effect 0.5 (-1.0, 0); favours IV iron Exercise duration: mean (95% CI) treatment effect 43 (-66, 153); no difference	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to CHF patients with iron deficiency.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Anker 2009 was multicentre (11 countries), Okonko 2008 was conducted in UK and Poland.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One level II study with a low risk of bias and one level II study with a high risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	B	Substantial
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.18 In CHF patients (NYHA functional classes II or III) with iron deficiency (absolute and functional), IV iron improves functional or performance status, independent of Hb concentration.

6MWT, 6 Minute Walk test; CHF, chronic heart failure; CI, confidence interval; EQ-5D, EuroQol-5 dimensions; IV, intravenous; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; SD, standard deviation

Key question(s): In anaemic patients with CKD, what is the effect of ESAs vs no ESAs on mortality?			Evidence Matrix: EM3.P
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence: Cody 2005 (good quality; 3 trials [all fair], N=168; pre-dialysis; EPO vs no EPO); Tonelli 2008 (good quality; 7 trials [6 fair, 1 poor], N=1048; on-dialysis and pre-dialysis; ESA vs no ESA) **Level II evidence published after Tonelli 2008 literature review:** 2 RCTs: Macdougall 2007 (fair; N=196; pre-dialysis; EPO vs no EPO); Pfeffer 2009 (good; N=4038; type 2 diabetes and pre-dialysis CKD; DAR vs placebo)	CKD	CDK (pre dial + diab)	
	A	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
All the studies were consistent in finding no significant difference in overall mortality between treatment arms. There was no significant heterogeneity[a] in cardiovascular mortality (Tonelli 2008: P=0.84, I^2=0) or overall mortality (update of Tonelli 2008 meta-analysis: P=0.69, I^2=0). Pfeffer 2009 was the only study to report deaths attributable to cancer, deaths among patients with a history of malignant condition at baseline, and deaths attributable to cancer among patients with a history of malignant condition at baseline.	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only; CKD and type II diabetes)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
Update of Tonelli 2008 meta-analysis (overall mortality): haemodialysis CKD (N=740; RR 0.70; 95% CI: 0.39, 1.26), peritoneal dialysis CKD (N=152; RR 1.90; 95% CI: 0.18, 20.49); pre-dialysis CKD (N=352; RR 0.38; 95% CI: 0.09, 1.55), pre-dialysis CKD with type 2 diabetes (N=4038; RR 1.05; 95% CI: 0.93, 1.19), overall CKD (N=5282; RR 1.02; 95% CI: 0.91, 1.15) **Cardiovascular mortality (Tonelli 2008):** pre-dialysis (N=73; RR 0.15; 95% CI: 0.01, 2.99), haemodialysis (N=491; RR 0.16; 95% CI: 0.03, 0.88; Favours ESA), overall CKD (N=564; RR 0.15; 95% CI: 0.03, 0.69; Favours ESA) **Results from Pfeffer 2009:** Deaths attributable to cancer (N=4038; 1.9% vs 1.2%; P=0.08; non-significantly favours placebo), deaths among patients with a history of malignant condition at baseline (N=348; 31.9% vs 23.1%; P=0.13; non-significantly favours placebo), deaths attributable to cancer among patients with a history of malignant condition at baseline (N=348; 7.4% vs 0.6%; P=0.0002; Favours placebo)	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Good quality evidence with no effect
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results for overall mortality are generalisable to all adult patients with CKD. The results for cardiovascular mortality and deaths attributable to cancer among patients with a history of malignant condition are dependent on whether the patients are on dialysis.	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

All-cause mortality: the studies were conducted in UK, Canada, Japan, USA, Germany, and Eastern Europe. Pfeffer 2009 was multicentre with 623 sites in 24 countries including Australia.
Cardiovascular mortality: The studies were conducted in Japan in non-dialysis dependent CKD patients, and Germany and Eastern Europe for haemodialysis patients.

A	A	Evidence directly applicable to Australian healthcare context
B	B	Evidence applicable to Australian healthcare context with few caveats
C	C	Evidence probably applicable to Australian healthcare context with some caveats
D	D	Evidence not applicable to Australian healthcare context

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

For the CKD etc group, the findings were based on a single, large, multicentre RCT (which included Australia). Therefore, given that all other components in the evidence matrix were rated 'A', the overall grade is an 'A'.
All patients were treated to a low to intermediate haemoglobin target.

EVIDENCE STATEMENT MATRIX

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

Component		CKD	CKD (pre-dialysis + type II diabetes + history of malignant	Description
1.	Evidence base	B	B	One level II study with a low risk of bias in patients with CKD and type II diabetes. Several level II studies with a moderate risk of bias in patients with CKD alone.
2.	Consistency	A	NA	All studies in CKD patients consistent for overall mortality. Only one study in patients with CKD and type II diabetes.
3.	Clinical impact	NA	A	No difference between treatment arms for overall mortality. A much higher incidence of cancer specific mortality in pre-dialysis CKD patients with type II diabetes and a history of malignant condition at baseline.
4.	Generalisability	B	A	Overall, the evidence is directly generalisable to CKD patients with some caveats. The results from Pfeffer 2009 are directly generalisable to CKD patients with type II diabetes.
5.	Applicability	A	A	Evidence directly applicable to Australian healthcare context

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.19 In anaemic patients with CKD, the effect of ESA therapy to a Hb target of 100–110 g/L on mortality is uncertain compared with no ESA therapy.
ES3.20 In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignant condition at baseline, ESAs increase the incidence of mortality attributable to cancer.

CI, confidence interval; CKD, chronic kidney disease; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; NA, not applicable; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with CKD, what is the effect of ESA vs no ESA on transfusion?		Evidence Matrix: EM3.Q
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: Cody 2005 (good quality; 3 trials [all fair], N=111; pre-dialysis; EPO vs no EPO); Tonelli 2008 (good quality; 3 trials [all fair], N=300; on-dialysis and pre-dialysis; ESA vs no ESA)[a] Level II evidence published after Tonelli 2008 literature review: 1 RCT: Pfeffer 2009 (good; N=4038; type 2 diabetes and pre-dialysis CKD; DAR vs placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Although some of the studies were not statistically significant, all the studies agreed in direction (ie, favouring ESAs). There was no significant heterogeneity[b] in the Cody et al (200) review (P=0.60; I^2=0.0%). There was substantial heterogeneity[b] in the on-haemodialysis patients in the Tonelli 2008 review (P=0.13; I^2=56.2%). Pfeffer 2009 was the only study in CKD patients with type 2 diabetes.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
RBC transfusion incidence Cody 2005 (EPO vs no EPO): Pre-dialysis (N=111[a]; 6.6% vs 26.0%; RR 0.32; 95% CI: 0.12, 0.83; Favours EPO) Tonelli 2008 (ESA vs no ESA): Pre-dialysis (N=83[a]; 9.3% vs 22.5%; RR 0.41; 95% CI: 0.14, 1.24); haemodialysis (N=217; 5.3% vs 59.3%; RR 0.09; 95% CI: 0.03, 0.32; Favours ESA) Results from Pfeffer 2009 (DAR vs placebo; N=4038): 14.8% vs 24.5%; HR 0.56; 95% CI: 0.49, 0.65; Favours DAR)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to adult patients with pre-dialysis CKD treated with EPO or adult patients with type 2 diabetes and pre-dialysis CKD treated with DAR.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Cody 2005: all studies were conducted in the USA Tonelli 2008 (pre-dialysis): The study was conducted in the USA Tonelli 2008 (haemodialysis): The studies were conducted in Germany and Canada Pfeffer 2009: A multicentre study conducted at 623 sites in 24 countries, including Australia	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One level II study with low risk of bias and several level II studies with a moderate risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	A	Very large
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	A	Evidence directly applicable to Australian healthcare context

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

3.21 In anaemic patients with CKD, ESA therapy to a Hb target of 100–110 g/L reduces RBC transfusion incidence compared with no ESA therapy.

CI, confidence interval; CKD, chronic kidney disease; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HR, hazard ratio; NA, not applicable; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk

[a] Two of the three RCTs reported in Cody et al (2005) were excluded from Tonelli et al (2008) because they had a sample size of less than thirty. Similarly, two of the three RCTs reported in Tonelli et al (2008) were excluded from the Cody et al (2005) review because they were conducted in patients undergoing haemodialysis.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with CKD, what is the effect of ESAs vs no ESAs on thromboembolic events?			Evidence Matrix: EM3.R
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence: Tonelli 2008 (good quality; ESA vs no ESA): MI (2 trials [1 poor, 1 fair], N=445; 1 haemodialysis, 1 pre-dialysis); stroke (1 trial [fair], N=129; haemodialysis CKD); vascular access thrombosis (1 trial [fair], N=118; haemodialysis CKD). Level II evidence published after Tonelli 2008 literature review: 1 RCT: Pfeffer 2009 (good; N=4038; type 2 diabetes and pre-dialysis CKD; DAR vs placebo).	Stroke and other	MI	
	A	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
MI: None of the studies found a significant difference between treatment arms, and all the studies favoured ESA. There was no significant heterogeneity[a] in the Tonelli 2008 review (P=0.68; I^2=0). Stroke: The Bahlmann 1991 study (identified by Tonelli 2008) found no significant difference between treatment arms (but favoured ESA), in Pfeffer 2009 there was a significantly lower incidence of stroke in the placebo arm. Vascular access thrombosis, venous thromboembolic events, arterial thromboembolic events: NA (one study only)	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
MI: Tonelli 2008 (N=445; 0.9% vs 1.8%; RR 0.56; 95% CI 0.12, 2.62); Pfeffer 2009 (N=4038; 6.2% vs 6.4%; HR 0.96; 95% CI 0.75, 1.22) Stroke: Tonelli 2008 (N=129; 0.0% vs 1.5%; RR 0.35; 95% CI 0.01, 8.41); Pfeffer 2009 (N=4038; 5.0% vs 2.6%; HR 1.92; 95% CI 1.38, 2.68; Favours placebo) Vascular access thrombosis: Tonelli 2008 (N=118; RR 5.64; 95% CI 0.75, 42.16; non-significantly favours no ESAs) Myocardial ischemia: Pfeffer 2009 (N=4038; 2.0% vs 2.4%; HR 0.84; 95% CI 0.55, 1.27) Venous thromboembolic events: Pfeffer 2009 (N=4038; 2.0% vs 1.1%; P=0.02; Favours placebo) Arterial thromboembolic events: Pfeffer 2009 (N=4038; 8.9% vs 7.1%; P=0.04; Favours placebo)	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results are generalisable to adult patients with pre-dialysis CKD treated with EPO or adult patients with type 2 diabetes and pre-dialysis CKD treated with DAR.	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
MI: Eastern Europe, USA, and multicentre (including Australia; Pfeffer 2009) Stroke: Germany and multicentre (including Australia; Pfeffer 2009) HF: Eastern Europe and USA Vascular access thrombosis: Canada Myocardial ischemia: multicentre (including Australia; Pfeffer 2009) Venous thromboembolic events: multicentre (including Australia; Pfeffer 2009) Arterial thromboembolic events: multicentre (including Australia; Pfeffer 2009)	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*			

EVIDENCE STATEMENT MATRIX

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

Component	Stroke and other	MI	Description
1. Evidence base	B	B	Several level II studies with a moderate risk of bias in CKD patients. One level II study with a low risk of bias in CKD patients with type II diabetes.
2. Consistency	B	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	B	B	Substantial
4. Generalisability	B	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	A	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.22 In anaemic patients with CKD, targeting a Hb concentration above 130 g/L with ESA therapy increases the incidence of stroke and other thromboembolic events The effect of targeting lower Hb concentrations is uncertain

ES3.23 In anaemic patients with CKD, ESA therapy to a Hb target of 100–110 g/L does not appear to affect the incidence of MI.

CI, confidence interval; CKD, chronic kidney disease; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; MI, myocardial infarction; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with CKD, what is the effect of ESAs vs no ESAs on functional/performance status?		Evidence Matrix: EM3.S
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: Tonelli 2008 (good quality; ESA vs no ESA): KDQ (1 trial [fair], N=98; haemodialysis CKD) Level II evidence published after Tonelli 2008 literature review: 3 RCTs: Cianciaruso 2008 (good; N=78; pre-dialysis CKD; EPO vs no EPO); Macdougall 2007 (fair; N=196; pre-dialysis CKD; EPO vs no EPO); Pfeffer 2009 (good; N=3531 [FACT] or 2295 [SF-36]; type 2 diabetes and pre-dialysis CKD; DAR vs placebo).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The disparate measures of functional/performance status used in the identified studies prevents a direct comparison of heterogeneity. HRQL In CESG 1990 (from Tonelli 2008), EPO significantly improved HRQL as measured by KDQ. Pfeffer 2009 found that DAR significantly improved FACT-fatigue compared with control, but there was no significant impact on change in SF (energy or physical functioning). NYHA and CCS status Cianciaruso 2008 found no significant difference in the change of NYHA and CCS status between treatment arms.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Change in KDQ (fatigue) from baseline: Tonelli 2008 (N=98; MD 1.10; 95% CI 0.76, 1.44; P<0.001; Favours ESA) Mean (SD) change in FACT (fatigue) from baseline: Pfeffer 2009 (N=3531; 4.2 [10.5] vs 2.8 [10.3]; P<0.001; Favours DAR) Patients with an increase of 3 or more points on the FACT (fatigue) from baseline: Pfeffer 2009 (N=3531; 54.7% vs 49.5%; P=0.002; Favours DAR) Mean (SD) change in SF (energy) from baseline: Pfeffer 2009 (N=2295; 2.6 [9.9] vs 2.1 [9.7]; P=0.20) Mean (SD) change in SF (physical functioning) from baseline: Pfeffer 2009 (N=2295; 1.3 [9.2] vs 1.1 [8.8]; P=0.51) Patients with a decline in NYHA status from baseline: Cianciaruso 2008 (N=78; 5.4% vs 2.4%; P=0.609) Patients with a decline in CCS status from baseline: Cianciaruso 2008 (N=78; 0.0% vs 4.9%; P=0.495) Mean (SD) last recorded distance for 6MWT: Macdougall 2007 (N=196; 419.3 [124.4] vs 420.5 [129.0]; P=0.954) Mean (SD) worst result for 6MWT: Macdougall 2007 (N=196; 395.8 [110.5] vs 408.4 [127.8]; P=0.526)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Quality of life (fatigue): generalisable to CKD patients on haemodialysis and pre-dialysis CKD patients with type 2 diabetes. SF (energy and physical functioning): generalisable to pre-dialysis CKD patients with type 2 diabetes. NYHA and CCS status: generalisable to pre-dialysis CKD patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
QoL (fatigue): Canada and multicentre (including Australia; Pfeffer 2009) SF (energy and physical functioning): multicentre (including Australia; Pfeffer 2009) NYHA and CCS status: Italy Exercise capacity: Canada and UK	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats (haemodialysis CKD and pre-dialysis CKD with type II diabetes)
	C	Evidence probably applicable to Australian healthcare context with some caveats (NYHA and CCS status in patients with pre-dialysis CKD)
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
Clinical impact	C	Moderate clinical impact
Generalisability	B	Evidence directly generalisable to target population with some caveats
Applicability	A	Evidence directly applicable to Australian healthcare context

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.24 In nondiabetic dialysis patients, compared to no treatment, ESA therapy targeted to a Hb ≥95 g/L may reduce fatigue and improve physical functioning.

ES3.25 In anaemic patients with non dialysis-dependent CKD, ESA therapy to a Hb target of 100–110 g/L may reduce fatigue, but has little impact on physical functioning.

6MWT, 6-minute walk test; CESG, Canadian Erythropoietin Study Group; CCS, Canadian Cardiovascular Society; CI, confidence interval; CKD, chronic kidney disease; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy; Hb, haemoglobin; HF, heart failure; HRQL, health related quality of life; KDQ, Kidney Disease Questionnaire; MD, mean difference; NA, not applicable; NYHA, New York Heart Association; QoL, quality of life; RR, relative risk; SD, standard deviation; SF, Short Form Health Survey

Key question(s): In anaemic patients with CKD, what is the effect of IV iron vs no IV iron on mortality?		Evidence Matrix: EM3.T
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 2 RCTs: Provenzano 2007 (fair quality; N=230; on-dialysis; IV vs oral); Stoves 2001 (poor quality; N=45; pre-dialysis; IV vs oral)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The studies were consistent in finding no significant difference in overall mortality between treatment arms. There was no significant heterogeneity[a] in all-cause mortality (P=0.26, I^2=20).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Meta-analysis: Mortality (N=259; 1.5% vs 2.2%; RR 0.78; 95% CI 0.10, 6.28; no significant difference)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results for overall mortality are generalisable to adult patients with CKD. Evidence includes both pre-dialysis and on-dialysis patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Provenzano 2009: a multicentre studies conducted in the USA. Stoves 2001: single centre study in the UK	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies were not powered to detect a significant difference in mortality.
Patients in the Provenzano 2009 were given constant ESA treatment, while patients in Stoves 2001 were treated with EPO to maintain an Hb level between 120 to 140 g/L.

EVIDENCE STATEMENT MATRIX

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

Component	Ratin	Description
Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
Consistency	B	Most studies consistent and inconsistency can be explained
Clinical impact	NA	Not applicable/no difference/underpowered
Generalisability	B	Evidence directly generalisable to target population with some caveats
Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.26 In anaemic patients with CKD receiving ESAs, the effect of IV iron on mortality is uncertain.

CI, confidence interval; CKD, chronic kidney disease; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; IV, intravenous; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with CKD, what is the effect of IV iron vs no IV iron on transfusion?			Evidence Matrix: EM3.U
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level II evidence: 2 RCTs: Singh 2006 (poor quality; N=126; on peritoneal dialysis; IV iron vs no iron); Van Wyck 2005 (poor quality; N=188; pre-dialysis; IV iron vs oral iron)	On-dialysi	Pre-dialysis	
	A	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low
	C	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
NA	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
Meta-analysis: patients requiring an anaemia intervention[a] (N=303; RR 0.43; 95% CI: 0.06, 3.36; no significant difference) Results from Singh 2006 (IV vs no iron): patients requiring an anaemia intervention[a] (N=121; 1.3% vs 10.9%; P = 0.05; favours IV iron). Results from van Wyck 2005 (IV vs Oral): patients requiring an anaemia intervention[a] (N=182; 8.8% vs 8.8%; P = 1.00; no significant difference).	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
SINGH The results are direct generalisable to adult patients on peritoneal dialysis VAN WYCK The results are generalisable to adult patients with CKD.	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Singh 2006: a multinational study conducted at 21 sites Van Wyck 2005: a multicentre study conducted at 35 sites in the USA	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare context

N
A

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

N
A

Patients in the Singh 2006 were treated with constant ESA. While patients in Van Wyck 2005 were treated with iron therapy with or without ESA treatment.

Furthermore patients in the control arm, no iron supplementation, did not receive placebo or other iron treatment. This could influence the higher incidence for blood transfusion (anaemia intervention) in this group.

The need for blood transfusion was measured in Singh 2006 and Van Wyck 2005 by 'Anaemia intervention'. 'Anaemia intervention' was defined as either: an increase in ESA dose, non-protocol IV iron or RBC transfusion, resulting in non-completion of study. None of the studies reported volumes of blood transfusions. The analysis is based on indirect measure for blood transfusion frequency.

EVIDENCE STATEMENT MATRIX

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

Component	On-dialysis	Pre-dialysis	Description
Evidence base	D	D	Two level II studies with a high risk of bias
Consistency	NA	NA	Evidence is inconsistent
Clinical impact	C	D	Moderate impact for on-dialysis CKD patients. No difference for pre-dialysis CKD patients.
Generalisability	A	B	Evidence directly generalisable to target population with some caveats
Applicability	B	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.27 In anaemic patients with CKD on dialysis and receiving ESAs, IV iron may reduce the need for an anaemia intervention.
ES3.28 In anaemic patients with non dialysis-dependent CKD, the effect of IV iron on RBC transfusion requirement is uncertain.

CI, confidence interval; CKD, chronic kidney disease; IV, intravenous; ESA, erythropoiesis stimulating agent; NA, not applicable; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk

[a] The need for blood transfusion was measured in Singh 2006 and Van Wyck 2005 by 'Anaemia intervention'. 'Anaemia intervention' was defined as either: an increase in ESA dose, non-protocol IV iron or RBC transfusion, resulting in non-completion of study.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Key question(s): In anaemic patients with CKD, what is the effect of IV iron vs no IV iron on functional/performance status?		Evidence Matrix: EM3.V
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 2 RCTs: Agarwal 2006 (good quality; N=75; pre-dialysis; IV iron vs oral iron); Van Wyck 2005 (poor quality; N=182; pre-dialysis; IV iron vs oral iron)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The disparate measures of functional/performance status used in the identified studies prevents a direct comparison of heterogeneity. KDQoL (SF-12) Agarwal 2006 found significant improvements in KDQoL scores within the IV arm. The significant improvement in KDQoL was restricted to two measures (Symptoms of KD and Effects of KD). No significant differences were reported in the other measures (such as SF-12 physical health composite, SF-12 mental health composite and Burden of KD) between IV and oral therapy. SF-36 Van Wyck 2005 found no significant difference in the change of SF-36 between treatment arms.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Results from Agarwal 2006 (IV vs no iron): Iron-deficient, anaemic, on-dialysis CKD, no ESA treatment. Mean [SD] KDQoL change from baseline,%: • SF-12 physical health composite (N=75; 4.8 [8.6] vs 0.7 [8.6], P=0.080; No significant difference • SF-12 mental health composite (N=75; 3.3 [9.8] vs -0.8 [15.1], P=0.114; No significant difference • Burden of KD (N=75; 6.4 [19.6] vs -3.6 [25.9], P=0.056; No significant difference • Symptoms of KD (N=75; 3.0 [11.6] vs -2.7 [17.5], P=0.025; Favours IV • Effects of KD (N=75; 2.7 [14.5] vs -2.3 [13.13], P=0.048; Favours IV Results from Van Wyck 2005 (IV vs Oral): Pre-dialysis CKD and ESA/no ESA treatment (N=182; NR; P = NR; No significant difference).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to adult patients with CKD. Both studies were in pre-dialysis CKD patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
KDQoL (including SF-12): a multicentre study conducted at 26 sites in the USA SF-36: a multicentre study conducted at 35 sites in the USA	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
Consistency	B	Most studies consistent and inconsistency can be explained
Clinical impact	D	Slight/restricted
Generalisability	B	Evidence directly generalisable to target population with some caveats
Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.29 In anaemic patients with non dialysis-dependent CKD, IV iron therapy may improve functional or performance status compared to oral iron therapy.

CI, confidence interval; CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; IV, intravenous; KDQoL, Kidney Disease quality of life; KD, Kidney Disease; NA, not applicable; QoL, quality of life; RR, relative risk; SD, standard deviation; SF, Short Form Health Survey

Key question(s): In elderly patients with anaemia, what is the effect of ESAs vs no ESAs on mortality?		Evidence Matrix: EM3.W
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 cross-over RCT: Agnihotri 2007 (poor quality; Phase I N=58; Phase II N=54; EPO vs placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Phase I 3.1% vs 3.8%; RR 0.81; 95% CI 0.05, 13.55; no difference Phase II 0% vs 0%; no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Somewhat generalisable to elderly patients with anaemia. But the study population was small, and mainly African-American.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The study was not powered to detect a significant difference in mortality.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.30 In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on mortality is uncertain.

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

Key question(s): In elderly patients with anaemia, what is the effect of ESAs vs no ESAs on thromboembolic events?		Evidence Matrix: EM3.X
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 cross-over RCT: Agnihotri 2007 (poor quality; Phase I N=58; Phase II N=54; EPO vs placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Phase I DVT: 0% vs 3.8%; RR 0.26 (0.01, 6.69) Pulmonary embolism: 0% vs 0% Stroke: 0% vs 3.8%; RR 0.26 (0.01, 6.69) Phase II DVT: 0% vs 0% Pulmonary embolism: 4.2% vs 0%; RR 3.89 (0.15, 99.97) Stroke: 0% vs 0%	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Somewhat generalisable to elderly patients with anaemia. But the study population was small, and mainly African-American.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The study was not powered to detect a significant difference in thromboembolic events.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.31 In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on thromboembolic events is uncertain.

DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

Key question(s): In elderly patients with anaemia, what is the effect of ESAs vs no ESAs on functional/performance status?		Evidence Matrix: EM3.Y
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 cross-over RCT: Agnihotri 2007 (poor quality; Phase I N=58; Phase II N=54; EPO vs placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Phase I Mean (SE) FACIT-anaemia (fatigue subscale): 41.9 (1.0) vs 36.4 (1.1); Favours EPO Mean (SE) FACIT-anaemia (anaemia subscale): 62.3 (1.2) vs 56.3 (1.4); Favours EPO Mean (SE) FACIT-anaemia (total): 146.8 (2.6) vs 137.9 (2.9); Favours EPO Mean (SE) FACT-general: 85.1 (1.5) vs 81.6 (1.6); No significant difference Mean (SE) Tug test, sec: 27.9 (2.8) vs 27.9 (3.2); No significant difference Phase II Mean (SE) FACIT-anaemia (fatigue subscale): 43.4 (2.3) vs 33.8 (2.0); Favours EPO Mean (SE) FACIT-anaemia (anaemia subscale): 64.3 (2.8) vs 53.6 (2.4); Favours EPO Mean (SE) FACIT-anaemia (total): 152.2 (5.3) vs 132 (4.6); Favours EPO Mean (SE) FACT-general: 87.9 (2.9) vs 78.4 (2.4); Favours EPO Mean (SE) Tug test, sec: 23.8 (1.7) vs 24.5 (1.5); No significant difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Somewhat generalisable to elderly patients with anaemia. But the study population was small, and mainly African-American.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One Level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/restricted
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.32 In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on functional or performance status is uncertain.

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; FACT, Functional Assessment of Cancer Therapy; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

Key question(s): In HCV-infected patients who developed anaemia following combination therapy, what is the effect of ESAs vs no ESAs on mortality?		Evidence Matrix: EM3.Z
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 RCT: Afdhal 2004 (fair quality; N=185; EPO vs placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
1.1% vs 0%; RR 2.97; 95% CI 0.12, 71.93; no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with HCV who have developed anaemia following combination therapy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The study was not powered to show a significant difference in mortality.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

The CRG considered that there was insufficient evidence on which to base an evidence statement.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HCV, hepatitis C virus; NA, not applicable; RR, relative risk

Key question(s): In HCV-infected patients who developed anaemia following combination therapy, what is the effect of ESAs vs no ESAs on thromboembolic events?		Evidence Matrix: EM3.AA
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 RCT: Afdhal 2004 (fair quality; N=185; EPO vs placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Cerebrovascular disorder/cerebral thrombosis: 1.1% vs 0%; RR 2.97; 95% CI 0.12, 71.93; no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with HCV who have developed anaemia following combination therapy.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The study was not powered to show a significant difference in thromboembolic events.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

The CRG considered that there was insufficient evidence on which to base an evidence statement.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HCV, hepatitis C virus; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

Key question(s): In HCV-infected patients who developed anaemia following combination therapy, what is the effect of ESAs vs no ESAs on functional/performance status?			Evidence Matrix: EM3.AB
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level II evidence: 2 RCTs: Afdhal 2004 (fair quality; N=185; EPO vs placebo); Dieterich 2003 (poor quality; N=64; EPO vs standard care)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
EPO significantly improved SF-36 (physical functioning, physical and emotional role, bodily pain, vitality, social functioning, and mental health; not general health subscale) compared with control in Afdhal 2004 but did not improve SF-12 (physical component, mental component) in Dieterich 2003.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
SF-36: Afdhal 2004: EPO led to a significantly (P<0.05) greater improvement, compared with control, for the physical functioning, role (physical and emotional), bodily pain, vitality, social functioning, and mental health subscales; but not the general health subscale. (Note: Eight domains, each with a score of 100) SF-12: Dieterich 2003: No significant difference between treatment arms for either the physical or mental components.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The results are generalisable to patients with HCV who have developed anaemia following combination therapy.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to	

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EPO appears to help maintain antiviral dosage in some HCV patients, but this was not specifically addressed in the guideline development.

EVIDENCE STATEMENT MATRIX

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

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

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

The CRG considered that there was insufficient evidence on which to base an evidence statement.

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HCV, hepatitis C virus; NA, not applicable; SF, Short Form Health Survey

Key question(s): In anaemic patients with HIV, what is the effect of ESAs vs no ESAs on mortality?		Evidence Matrix: EM3.AC
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: Marti-Carvajal 2007 (good quality; 1 trial [fair]; N=63; EPO vs placebo) No subsequently published Level II evidence	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
0% vs 5.9%; RR 0.23; 95% CI 0.01, 4.67; no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Treatment of HIV/AIDS has changed dramatically since 1990.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The study was not powered to detect a significant difference in mortality.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

The CRG considered that there was insufficient evidence on which to base an evidence statement.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HIV, human immunodeficiency virus; NA, not applicable; RR, relative risk

Key question(s): In anaemic patients with HIV, what is the effect of ESAs vs no ESAs on transfusion?		Evidence Matrix: EM3.AD
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: Marti-Carvajal 2007 (good quality; 1 trial [fair]; N=63; EPO vs placebo) No subsequently published Level II evidence	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Incidence of allogeneic blood transfusion: 37.9% vs 61.8%; P>0.05 Incidence of allogeneic blood transfusion (patients with endogenous EPO **≤500 IU/L)**: 5/NR vs 17/NR; P<0.05; Favours EPO Mean (SD) volume of whole blood transfused, units: 1.48 (NR) vs 2.58 (NR); P>0.05 **Mean (SD) volume of RBC or whole blood transfused (patients with endogenous EPO ≤500** IU/L), units: 0.84 (NR) vs 2.74 (NR); P<0.05; Favours EPO	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Treatment of HIV/AIDS has changed dramatically since 1990.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One Level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/restricted
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

The CRG considered that there was insufficient evidence on which to base an evidence statement.

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HIV, human immunodeficiency virus; NA, not applicable; NR, not reported; RBC, red blood cell; SD, standard deviation

Key question(s): In anaemic patients with HIV, what is the effect of ESAs vs no ESAs on functional/performance status?		Evidence Matrix: EM3.AE
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: Marti-Carvajal 2007 (good quality; 1 trial [poor]; N=66; EPO vs placebo) No subsequently published Level II evidence	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Mean (SD) change in SF-12 (physical component): 6.0 (1.8) vs 2.2 (1.2); P=NR Mean (SD) change in SF-12 (mental component): 2.3 (2.0) vs 0.1 (1.5); P=NR	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Somewhat generalisable to anaemic patients with HIV, but the study population was small and few baseline demographics were reported.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/restricted
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

The CRG considered that there was insufficient evidence on which to base an evidence statement.

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HIV, human immunodeficiency virus; NA, not applicable; NR, not reported; SF-12, Short Form (36) Health Survey; SD, standard deviation

Key question(s): In IBD patients with iron deficiency anaemia, what is the effect of IV iron vs no IV iron on mortality?		Evidence Matrix: EM3.AF
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 RCT: Kulnigg 2008 (fair quality; N=200; IV iron vs oral iron)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
0.7% vs 0.0%; RR 1.39; 95% CI: 0.06, 33.69; no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to IBD patients with iron deficiency anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Kulnigg 2008 was multicentre (Europe, Mexico, and Argentina)	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The study was not powered to detect a difference in mortality.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One level II study with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.33 In IBD patients with iron deficiency anaemia, the effect of IV iron versus oral iron on mortality is uncertain.

CI, confidence interval; IBD, inflammatory bowel disease; IV, intravenous; NA, not applicable; RCT, randomised controlled trial; RR, relative risk

Key question(s): In IBD patients with iron deficiency anaemia, what is the effect of IV iron vs no IV iron on functional/performance status?		Evidence Matrix: EM3.AG
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 2 RCTs: Kulnigg 2008 (fair quality; N=196; IV iron vs oral iron), Schroder 2005 (poor quality; N=46[a]; IV iron vs oral iron)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The studies agree in direction for SF-36. Only Schroder 2005 reported CAI and CDAI	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Kulnigg 2008 Median change in SF-36: 14.1 vs 8.6; P=NR Schroder 2005 Median (range) CDAI at follow-up: 74 (23 to 279) vs 78 (0 to 353); P=NR Median (range) CAI at follow-up: 5 (1 to 9) vs 3 (0 to 5); P=NR Median (range) SF-36 at follow-up: 108.0 (100.0 to 116.5) vs 116.0 (108.0 to 120.0); P=NR	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to IBD patients with iron deficiency anaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Kulnigg 2008 was multicentre (Europe, Mexico, and Argentina); Schroder 2005 was conducted in Germany	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Unclear whether patients were iron replete or not

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One level II study with a moderate risk of bias one level II study with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.34 In IBD patients with iron deficiency anaemia, it is uncertain whether there is any difference between the effects of IV iron and oral iron on functional or performance status.

CAI, Colitis Activity Index; CDAI, Crohn's Disease Activity Index; IBD, inflammatory bowel disease; IV, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SF-36, Short-Form (36)

[a] Only subgroups of this study population underwent assessment for functional performance status: N=26 for CDAI; N=17 for CAI; N=NR for SF-36

Key question(s): In anaemic patients with MDS, what is the effect of ESAs vs no ESAs on mortality?		Evidence Matrix: EM3.AH
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 2 RCTs: Greenberg 2009 (poor quality; N=110; EPO vs standard care); Thompson 2000 (poor quality; N=66; EPO + GM-CSF vs placebo + GM-CSF)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
Neither of the studies found a significant difference between treatment arms in mortality or overall survival.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Greenberg 2009: Mortality: 71.7% vs 84.2%; HR 0.77; 95% CI 0.48, 1.24; no difference Mortality (RARS MDS subgroup analysis; N=37): 60.0% vs 88.2; HR 0.41; 95% CI 0.18, 0.96; favours control No significant differences were found between treatment arms for subgroup analyses of mortality by gender, age, MDS subtypes other than RARS MDS (ie, RA and RAEB), patients with/without previous transfusion, endogenous EPO at baseline, and IPSS score. Thompson 2000: Mortality: 6.7% vs 0%; HR 3.35; 95% CI 0.18, 62.03; no difference Meta-analysis of Greenberg 2009 and Thompson 2000: Mortality (N=176): 18.4% vs 11.5%; RR 1.90; 95% CI 0.93, 3.91; no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with anaemia of MDS	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Thompson 2000 was conducted in the USA. Greenberg 2009 was a multicentre (USA and Israel) trial.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies were not powered to detect a difference in mortality.

EVIDENCE STATEMENT MATRIX

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

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

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.35 In anaemic patients with MDS, the effect of ESAs on mortality is uncertain.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; GM-CSF, granulocyte macrophage colony-stimulating factor; HR, hazard ratio; IPSS, MDS, myelodysplastic syndrome; NA, not applicable; RA, refractory anaemia; RAEB, refractory anaemia with excess blasts; RARS, refractory anaemia with ring sideroblasts

Key question(s): In anaemic patients with MDS, what is the effect of ESAs vs no ESAs on transfusion?		Evidence Matrix: EM3.AI
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 RCT: Thompson 2000 (poor quality; N=66; EPO + GM-CSF vs placebo + GM-CSF)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
RBC transfusion incidence: 76% vs 90 %; RR 0.84; 95% CI 0.67, 1.04 **RBC transfusion incidence (baseline endogenous EPO ≤ 500 mU/mL; N=37):** 60% vs 92%; RR 0.65; 95% CI 0.46, 0.94; favours EPO Mean (SD) units of RBC transfused during Months 2 and 3: 7.6 (NR) vs 9.1 (NR); P=NR Mean (SD) units of RBC transfus**ed during Months 2 and 3 (baseline endogenous EPO ≤ 500** mU/mL): 5.9 (NR) vs 9.5 (NR); P=0.09	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with anaemia of MDS.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Thompson 2000 was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.36 In anaemic patients with MDS receiving GM-CSF, ESAs may reduce transfusion incidence compared with no ESAs.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; GM-CSF, granulocyte macrophage colony-stimulating factor; NA, not applicable; NR, not reported; MDS, myelodysplastic syndrome; RA, refractory anaemia; RAEB, refractory anaemia with excess blasts; RARS, refractory anaemia with ring sideroblasts; RBC, red blood cell; RR, relative risk

Key question(s): In anaemic patients with MDS, what is the effect of ESAs vs no ESAs on thromboembolic events?		Evidence Matrix: EM3.AJ
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 3 RCTs: Greenberg 2009 (poor quality; N=110; EPO vs standard care); Thompson 2000 (poor quality; N=66; EPO + GM-CSF vs placebo + GM-CSF); Ferrini 1998 (poor quality; N=87; EPO vs placebo)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
All of the studies agreed in direction, and none of the studies found a significant difference between treatment arms.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
DVT (Greenberg 2009; N=110): 1.8% vs 0%; RR 2.79; 95% CI 0.12, 67.10; no difference Meta-analysis of stroke (Thompson 2000 and Ferrini 1998; N=153): 2.2% vs 0%; RR 2.08; 95% CI 0.23, 18.84; no difference	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with anaemia of MDS.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Thompson 2000 was conducted in the USA. Ferrini 1998 was conducted in Italy. Greenberg 2009 was a multicentre (USA and Israel) trial.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies were not powered to detect a difference in thromboembolic events.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	D	Three level II studies with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.37 In anaemic patients with MDS, the effect of ESAs on thromboembolic events is uncertain.

CI, confidence interval; DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; GM-CSF, granulocyte macrophage colony-stimulating factor; MDS, myelodysplastic syndrome; NA, not applicable; RA, refractory anaemia; RAEB, refractory anaemia with excess blasts; RARS, refractory anaemia with ring sideroblasts; RR, relative risk

Key question(s): In anaemic patients with MDS, what is the effect of ESAs vs no ESAs on functional/performance status?		Evidence Matrix: EM3.AK
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 1 RCT: Greenberg 2009 (poor quality; N=84; EPO vs standard care)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
NA	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
FACT subscale and fatigue scores (at 4 months follow-up): N=84; No significant difference between treatment arms (P>0.05)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with anaemia of MDS	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Greenberg 2009 was a multicentre (USA and Israel) trial.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	D	One level II study with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES3.38 In anaemic patients with MDS, the effect of ESAs on functional or performance status is uncertain.

EPO, erythropoietin; ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy; MDS, myelodysplastic syndrome; NA, not applicable; RCT, randomised controlled trial

Recommendation(s) for the use of ESAs in cancer patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In cancer patients with anaemia, the *routine* use of ESAs is not recommended. If considered necessary, ESAs should be used with caution, balancing the increased risks of mortality and thromboembolic events against the reduced incidence and volume of transfusion.	A	EM3.A, EM3.B, EM3.C, EM3.D and EM3.E

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
ESAs are not currently TGA registered for this purpose.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?		
Include a requirement to utilise guidelines in the blood and blood product standard. Include in BloodSafe eLearning Include in presentations provided by CRG members at clinical meetings.		

Recommendation(s) for the treatment of iron deficiency in CHF patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In patients with CHF (NYHA functional classes II or III), identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status. *This is consistent with the 2011 Update to the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006* *Note: The studies reviewed only included patients treated with IV iron.*	B	EM3.O

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
While this may be a change in 'usual care' it is not a change in 'recommended practice'.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Should this recommendation be implemented, there would be REDUCED use of clinical, laboratory and blood product resources. This would be balanced with an increased cost associated with the use of iron, which is significantly cheaper than blood products.		
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Patients with CHF are likely to need to be treated with IV iron infusions.		
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
IV Iron Polymaltose can be used to deliver a total dose infusion but the infusion time is very slow (up to seven hours). There are limited data on the safety of delivery of this product over shorter timeframes. A more expensive IV product is currently being registered in Australia. Previously available IV iron preparations caused serious adverse reactions (anaphylaxis) and sometimes death. While these preparations are no longer available in Australia, there is residual clinical apprehension in the use of IV ion products.		
What could help to facilitate implementation of the recommendation?		
The NBA has organised a worshop is planned for March 2012 to explore barriers to the use of IV Ion and how to overcome these barriers. The output of this meeting will assist in the development of implementation of recommendations relating to IV iron therapy. Include a requirement to utilise guidelines in the blood and blood product standard. Include in BloodSafe eLearning Include in presentations provided by CRG members at clinical meetings.		

Recommendation(s) for the use of ESAs in patients with CKD

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In anaemic patients with CKD, ESA therapy to a Hb target of 100–110 g/L may be used to avoid blood transfusion, after consideration of risks and benefits for the individual patient. For comprehensive information about ESA therapy in patients with CKD, refer to CARI ESA guidelines (McMahon 2008)	B	EM3.Q

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
This recommendation aligns with the CARI recommendations and as such, does not represent a change to recommended practice.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?		
Include a requirement to utilise guidelines in the blood and blood product standard. Include in BloodSafe eLearning Include in presentations provided by CRG members at clinical meetings.		

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In anaemic patients with CKD, ESA therapy to a Hb target of 100–110 g/L may be used to relieve fatigue, after consideration of risks and benefits for the individual patient.	C	EM3.S

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
This recommendation aligns with the CARI recommendations and as such, does not represent a change to recommended practice.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?		
Include a requirement to utilise guidelines in the blood and blood product standard. Include in BloodSafe eLearning Include in presentations provided by CRG members at clinical meetings.		

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In anaemic patients with CKD, ESA therapy to a Hb target of over 130 g/L is not recommended because of increased morbidity.	B	EM3.R

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
This recommendation aligns with the CARI recommendations and as such, does not represent a change to recommended practice.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?		
Include a requirement to utilise guidelines in the blood and blood product standard. Include in BloodSafe eLearning Include in presentations provided by CRG members at clinical meetings.		

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and with a history of malignancy, the routine use of ESAs is not recommended because of the increased risk of cancer-related mortality.	B	EM3.P

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
This recommendation aligns with the CARI recommendations and as such, does not represent a change to recommended practice.		
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?		
Include a requirement to utilise guidelines in the blood and blood product standard. Include in BloodSafe eLearning Include in presentations provided by CRG members at clinical meetings.		

D4 Evidence – Question 4

Key question(s): In patients with acute pancreatitis, what is the effect of FFP vs no FFP on mortality?		Evidence Matrix: EM4.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 2 Level II studies of fair quality (Leese et al, 1987; Leese et al, 1991).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Neither study observed a significant difference between study arms in terms of mortality. This is probably due to the fact that both studies were inadequately powered to detect a significant difference in patient outcomes.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Due to the fact that both studies were inadequately powered to detect a significant difference in patient outcomes, the clinical impact is inestimable.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included studies examined patients with severe acute pancreatitis; however it is not sensible to apply the results to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Both studies were undertaken in a single UK hospital. Both studies are also reasonably old. The results are therefore of limited applicability to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
In the study by Leese et al (1987) the population did not have coagulopathy, while in the study by Leese et al (1991) it was not stated whether the population had coagulopathy.		
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	D	Evidence not applicable to Australian healthcare context
EVIDENCE STATEMENT ES4.1 In patients with acute pancreatitis, the effect of FFP on mortality is uncertain.		

FFP, fresh frozen plasma

Key question(s): In patients with acute pancreatitis, what is the effect of FFP vs no FFP on bleeding events?			Evidence Matrix: EM4.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes 2 Level II studies of fair quality (Leese et al, 1987; Leese et al, 1991).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
Neither study observed a significant difference between study arms in terms of mortality. This is probably due to the fact that both studies were inadequately powered to detect a significant difference in patient outcomes.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Due to the fact that both studies were inadequately powered to detect a significant difference in patient outcomes, the clinical impact is inestimable.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The included studies examined patients with severe acute pancreatitis; however it is not sensible to apply the results to the target population.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
Both studies were undertaken in a single UK hospital. Both studies are also reasonably old. The results are therefore of limited applicability to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
In the study by Leese et al (1987) the population did not have coagulopathy, while in the study by Leese et al (1991) it was not stated whether the population had coagulopathy.		
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	D	Evidence not applicable to Australian healthcare context
EVIDENCE STATEMENT ES4.2 In patients with acute pancreatitis, the effect of FFP on bleeding events is uncertain.		

FFP, fresh frozen plasma

Key question(s): In patients with liver disease, what is the effect of FFP vs no FFP on mortality?			Evidence Matrix: EM4.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes 1 Level II study of poor quality (Gazzard et al, 1975).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study did not detect a significant difference between study arms in terms of mortality. This result is probably due to the fact that the study was inadequately powered to detect significant differences for this outcome.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The included studies examined patients with prothrombin time ratio > 2.2 due to paracetamol overdose. The results are probably not generalisable to all patients with liver disease. It is not sensible to apply the results to the target population.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The included study was conducted at a single site in the UK and is now relatively old. The results are therefore probably of limited applicability to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.3 In patients with liver disease, the effect of FFP on mortality is uncertain.

FFP, fresh frozen plasma

Key question(s): In patients with liver disease, what is the effect of FFP vs no FFP on bleeding events?			Evidence Matrix: EM4.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes 1 Level II study of poor quality (Gazzard et al, 1975).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
NA	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study did not detect a significant difference between study arms in terms of bleeding events. This result is probably due to the fact that the study was inadequately powered to detect significant differences for this outcome.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The included studies examined patients with prothrombin time ratio > 2.2 due to paracetamol overdose. The results are probably not generalisable to all patients with liver disease. It is not sensible to apply the results to the target population.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The included study was conducted at a single site in the UK and is now relatively old. The results are therefore probably of limited applicability to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats
EVIDENCE STATEMENT ES4.4 In patients with liver disease, the effect of FFP on bleeding events is uncertain.		

FFP, fresh frozen plasma

Key question(s): In patients with haematological malignancies receiving chemotherapy, what is the effect of prophylactic platelet transfusion on mortality?		Evidence Matrix: EM4.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level II study of poor quality (Solomon et al, 1978); 1 Level III-2 study of fair quality (Khorana 2008); 1 Level IV study of poor quality (McCullough 2004)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The study by Solomon observed no significant difference between study arms for the outcome of mortality. This study was inadequately powered to detect any clinically or statistically significant differences in clinical outcomes between the study arms. The Level II study by Khorana found that transfusion was associated with a significant increase in the risk of in-hospital mortality (RR 2.40 95% CI 2.27, 2.52). The Level IV study by McCullogh reported a mortality rate of 4.3%.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study by Solomon was inadequately powered to detect a significant difference in patient outcomes. The study by Khorana reported a relative risk for mortality of (RR 2.40 95% CI 2.27, 2.52) for platelet transfusion compared to no transfusion.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The Level II study is in adult patients with acute lymphoblastic leukaemia. The Downey study was in elderly patients with traumatic brain injury. The Level II study was in hospitalised cancer patients and one third were aged 65 or over. The level IV study was in patients aged 6 or over with thrombocytopenia and included oncology patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The Level II study was undertaken in a single US hospital but is now reasonably old. The Level III study was conducted at 60 centres in the USA and the Level IV study was conducted at a single centre in Switzerland.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	C	Moderate
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.6 n patients with haematological malignancies receiving chemotherapy, the effect of prophylactic platelet transfusion on mortality is uncertain.

Key question(s): In patients with haematological malignancies receiving chemotherapy, what is the effect of prophylactic platelet transfusion on bleeding events?			Evidence Matrix: EM4.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes 1 Level II study of poor quality (Higby et al, 1974) and 1 Level IV study of poor quality (McCullough 2004).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
The study reported a non-significant trend towards lower incidence of bleeding events in patients receiving prophylactic transfusions compared to patients who were platelet poor (RR 0.38, 95% CI 0.13, 1.11; p=0.08). This study was small and was conducted in 1974. The level IV study reported rates of 58.0% for grade 2 bleeding and 5.1% for grade 3–4 bleeding in patients receiving platelet transfusions.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Higby (1974) reported a trend towards reduced bleeding events in patients who received platelets, although the study was underpowered.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The Level II study enrolled patients with acute myelocytic leukaemia. The level IV study was in patients aged 6 or over with thrombocytopenia and included oncology patients.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study by Higby et al (1974) is relatively old. The results are therefore applicable to the Australian setting with a few caveats. The level IV study was conducted at a single centre in Switzerland.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.7 In patients with haematological malignancies receiving chemotherapy, the effect of prophylactic platelet transfusion on bleeding events is uncertain.

Key question(s): What is the effect of platelet transfusion on transfusion-related adverse events?		Evidence Matrix: EM4.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
4 Level IV studies of poor quality (Heim 2008, McCullough 2004, Osselaer 2008 and Slichter 1997).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The level IV studies reported a range of rates for transfusion-related adverse events.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Although the Level IV studies did not provide comparative data on the incidence of transfusion-related adverse events in patients receiving platelet transfusion compared to patients receiving no transfusion, these results nonetheless inform the risk/benefit profile of platelet transfusion. The clinical impact is therefore considered to be substantial.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Heim 2008 included patients with haematological diseases or nonhematologic malignancies being treated with myeloablative chemotherapy or HSCT. McCullogh included patients with thrombocytopenia. Osselaer 2008 included patients with haematooncology diseases, surgical patients, critical care patients and outpatients. Slichter 1997 included patients receiving induction chemotherapy for acute myeloid leukemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The Level IV studies were carried out at centres in Switzerland, Belgium, Norway, Spain, Italy and the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.8 Platelet transfusions are associated with transfusion-related adverse events that can range from mild to serious.

Key question(s): In patients with cancer, what is the effect of platelet transfusion on mortality?		Evidence Matrix: EM4.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
1 Level III-2 study of fair quality (Khorana 2008)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The Level II study by Khorana found that transfusion was associated with a significant increase in the risk of in-hospital mortality (RR 2.40 95% CI 2.27, 2.52).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study by Khorana reported a relative risk for mortality of (RR 2.40 95% CI 2.27, 2.52) for platelet transfusion compared to no transfusion.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The Level III study was in hospitalised cancer patients and one-third were aged 65 or over.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The Level III study was conducted at 60 centres in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
Additional studies will not influence the decision		
EVIDENCE STATEMENT MATRIX *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.*		
Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
EVIDENCE STATEMENT ES4.9 In a broad population of hospitalised cancer patients, platelet transfusion may be associated with increased mortality, but causation has not been established.		

Key question(s): In patients with cancer what is the effect of platelet transfusion on transfusion-related adverse events?		Evidence Matrix: EM4.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level III-2 study of fair quality (Khorana 2008)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The Khorana study reported a significant increase in the risk of VTE (RR1.20; 95% CI 1.11, 1.29; p<0.001) and ATE (RR1.55; 95% CI 1.40, 1.71; p<0.001) with platelet transfusion compared to no transfusion.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The Khorana study enrolled hospitalised cancer patients. The study had more than one third of subjects aged 65 or over.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The level II study by Khorana was carried out at 6 centres in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	C	Moderate
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.10 In a broad population of hospitalised cancer patients, platelet transfusion may be associated with increased risk of thromboembolic events, but causation has not been established.

Key question(s): In patients receiving chemotherapy and prophylactic platelet transfusion, what is the effect of different platelet doses on mortality?		Evidence Matrix: EM4.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level II study of good quality (Slichter et al, 2010; n=1271)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The study found no significant difference between any of the assessed platelet doses for the outcome of mortality. Since the event rate was low, it is likely that the study was underpowered to detect differences between study arms for this outcome.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study was underpowered to detect differences between study arms for this outcome.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Patients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumours with platelet counts ≤10 x 10^{11}/L for 5 days or more. The results are probably generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken at a number of sites in the USA. The results are therefore applicable to the Australian setting with a few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.11 In patients receiving chemotherapy and prophylactic platelet transfusion, the effect of platelet dose on mortality is uncertain.

Key question(s): In patients receiving chemotherapy and prophylactic platelet transfusion, what is the effect of different platelet doses on bleeding events?			Evidence Matrix: EM4.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes two good quality studies (Slichter et al, 2010; Heddle et al, 2009) one fair quality study (Tinmouth et al, 2004) and one poor quality study (Sensebé et al, 2005)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
For the incidence of bleeding events with a WHO grade 2 or above, the large multicentre RCT by Slichter et al (2010) and the good quality RCT by Heddle et al (2009) found no significant difference between study arms in any of the dose comparisons presented. The fair quality study by Tinmouth et al (2004) found that there was a higher risk of experiencing a minor bleed in patients receiving 3 platelet units compared to 5 platelet units.	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
With the exception of the study by Tinmouth et al (2004) the studies all reported no effect of platelet dose on the incidence of bleeding events.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
Most of the studies included patients undergoing chemotherapy or stem cell population. While the exact populations may have differed slightly, the largest study (Slichter et al, 2010) is highly generalisable to the target population.	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*			
The largest good quality study by Slichter et al (2010) was undertaken at a number of sites in the USA. The results are therefore applicable to the Australian setting with a few caveats.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.12 In patients receiving chemotherapy and prophylactic platelet transfusion, platelet dose has no effect on bleeding events defined as mild or greater (WHO grade 2 or above).

WHO, World Health Organization

Key question(s): In patients receiving chemotherapy and prophylactic platelet transfusion, what is the effect of different platelet doses on transfusion-related adverse events?		Evidence Matrix: EM4.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 good quality Level II study (Slichter et al, 2010; n=1271) and one fair quality study (Goodnough et al, 2001)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The study by Slichter et al (2010) reported no significant difference in the incidence of serious adverse events, or adverse events occurring during or ≤4 hours after transfusion, for any of the assessed dose comparisons. Similarly, the study by Goodnough et al (2001) found no significant difference between study arms in the incidence of febrile transfusion reactions.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The largest study (Slichter et al, 2010) is highly generalisable to the target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Both studies were undertaken at a number of sites in the USA. The results are therefore applicable to the Australian setting with a few caveats.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES4.13 In patients receiving chemotherapy and prophylactic platelet transfusion, platelet dose does not appear to affect the incidence of transfusion-related adverse events.

Recommendation(s) for blood components

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE TABLE**
No recommendation made for this question.		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?	YES	NO

D5 Evidence – Question 5

Key question(s): In patients undergoing chemotherapy and haematopoietic stem cell transplantation, what is the effect of prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level on mortality?		Evidence Matrix: EM5.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: Includes one Level II study of good quality (Rebulla, 1997), one Level II study of fair quality (Diedrich 2005), and one poor quality Level II study (Zumberg, 2002).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
None of the included studies observed a significant difference between study arms for the outcome of mortality.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
It should be noted that some of the studies may have been inadequately powered to detect any clinically or statistically significant differences in mortality between the study arms.	*A*	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to patients undergoing chemotherapy and haematopoietic stem cell transplantation; however, some studies also included patients who were aged < 18 years.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The evidence is applicable to the Australian healthcare context; however two studies were more than 10 years old.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies by Rebulla et al (1997) and Zumberg et al (2002) assessed the effects of a transfusion trigger of 10 x 10^9/L compared to 20 x 10^9/L; however, it should be noted that the criteria for patients requiring rescue transfusion differed between all three studies. The study by Diedrich et al (2005) had the same restrictive transfusion trigger of 10 x 10^9/L in the intervention arm; however, the transfusion threshold in the control arm (30 x 10^9/L) was higher than that in the other three studies. It should be noted that studies had varying criteria for rescue transfusion and there were high rates of protocol violations in most cases. The exception to this was the study by Rebulla et al (1997), which had relatively low rates of protocol violations.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	D	Slight/restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.9 In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to the effect on mortality – the difference between a prophylactic platelet transfusion trigger of <10 × 10^9/L without risk factors or <20 × 10^9/L plus risk factors versus a higher trigger is uncertain. The effect at lower values is unknown.

Key question(s): In patients undergoing chemotherapy and haematopoietic stem cell transplantation, what is the effect of prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level on bleeding events?		Evidence Matrix: EM5.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II: Includes one Level II study of good quality (Rebulla, 1997), one Level II studies of fair quality (Diedrich 2005), and one poor quality Level II study (Zumberg, 2002).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
None of the included studies observed a significant difference between study arms for the outcome of bleeding events.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
None of the included studies observed a significant difference between study arms for the outcome of bleeding events.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to patients undergoing chemotherapy and haematopoietic stem cell transplantation; however, some studies also included patients who were aged < 18 years.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The evidence is applicable to the Australian healthcare context; however two studies were more than 10 years old.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies by Rebulla et al (1997), Heckman et al (1997) and Zumberg et al (2002) assessed the effects of a transfusion trigger of 10 x 10^9/L compared to 20 x 10^9/L; however, it should be noted that the criteria for patients requiring rescue transfusion differed between all three studies. The study by Diedrich et al (2005) had the same restrictive transfusion trigger of 10 x 10^9/L in the intervention arm; however, the transfusion threshold in the control arm (30 x 10^9/L) was higher than that in the other three studies. It should be noted that studies had varying criteria for rescue transfusion and there were high rates of protocol violations in most cases. The exception to this was the study by Rebulla et al (1997), which had relatively low rates of protocol violations.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	A	All studies consistent
3.	Clinical impact	D	Slight/restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.10 In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to major bleeding events – there is no difference between a prophylactic platelet transfusion trigger of <10 × 10^9/L without risk factors or <20 × 10^9/L plus risk factors and a higher trigger. The effect at lower values is unknown.

Key question(s): In patients undergoing chemotherapy and haematopoietic stem cell transplantation, what is the effect of prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level on RBC transfusion?		Evidence Matrix: EM5.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Rebulla, 1997) and two Level II studies of fair quality (Heckman, 1987 and Diedrich 2005).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
None of the included studies observed a significant difference between study arms for the mean number of RBC units transfused, or the mean number of RBC transfusions.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
None of the included studies observed a significant difference between study arms for the mean number of RBC units transfused, or the mean number of RBC transfusions	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to patients undergoing chemotherapy and haematopoietic stem cell transplantation; however, some studies also included patients who were aged < 18 years.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The evidence is applicable to the Australian healthcare context; however two studies were more than 10 years old.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies by Rebulla et al (1997), Heckman et al (1997) and Zumberg et al (2002) assessed the effects of a transfusion trigger of 10 x 10^9/L compared to 20 x 10^9/L; however, it should be noted that the criteria for patients requiring rescue transfusion differed between all three studies. The study by Diedrich et al (2005) had the same restrictive transfusion trigger of 10 x 10^9/L in the intervention arm; however, the transfusion threshold in the control arm (30 x 10^9/L) was higher than that in the other three studies. It should be noted that studies had varying criteria for rescue transfusion and there were high rates of protocol violations in most cases. The exception to this was the study by Rebulla et al (1997), which had relatively low rates of protocol violations.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2.	Consistency	A	All studies consistent
3.	Clinical impact	D	Slight/restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.11 In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to RBC transfusion – there is no difference between a prophylactic platelet transfusion trigger of <10 × 10^9/L without risk factors or <20 × 10^9/L plus risk factors and a higher trigger. The effect at lower values is unknown.

Key question(s): In patients with liver disease, what is the association between INR (or PT/APTT) level and the risk of mortality/survival?		Evidence Matrix: EM5.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one fair quality Level II study (Garden, 1985) one poor quality Level II study (Violi, 1995), one good quality Level III-3 study (Le Moine, 1992) and one fair quality Level III-3 study (Krige, 2009).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The trials measured a range of coagulation parameters, including absolute prothrombin ratio (PR), prothrombin time, partial thromboplastin time (aPPT) and international normalised ratio (INR). There was also some variation between studies in how the results were reported, with one study reporting the mean difference in the absolute prothrombin ratio in patients who survived and those who died (Garden et al, 1985), another reporting a regression coefficient for prothrombin time (Le Moine et al, 1992) and another reporting relative risk (Krige et al, 2009). All of the included studies, with the exception of one poor quality prospective cohort study (Violi et al, 1995) found that coagulopathy was an independent risk factor for mortality.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
All of the included studies, with the exception of one poor quality prospective cohort study (Violi et al, 1995) found that coagulopathy was an independent risk factor for mortality. In the study by Violi et al (1995), aPTT and prothrombin time were associated with survival in the univariate analysis but not in the multivariate analysis. The studies by Garden et al (1985) and Le Moine et al (1992) did not stratify patients according to their baseline clotting parameters; however, the study by Krige et al (2009) reported that an INR ≥ 2.3 was an independent risk factor for mortality (P=0.003).	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to patients with liver disease, although it should be noted that disease aetiology and symptoms varied considerably between studies.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The evidence is somewhat applicable to the Australian healthcare context; however most of the studies are now relatively dated.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

The studies by Garden et al (1985) and Le Moine et al (1992) did not stratify patients according to their baseline plotting parameters; however, the study by Krige et al (2009) reported that an INR ≥ 2.3 was an independent risk factor for mortality (P=0.003).

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	B	Substantial
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.1 In patients with liver disease, an elevated INR/PT/APTT level is independently associated with an increased risk of mortality.

INR, international normalised ratio; PT, prothrombin time, APTT, activated partial thromboplastin time

Key question(s): In patients with acute leukaemia, what is the association between INR (or PT/APTT) level and the risk of mortality?			Evidence Matrix: EM5.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one good quality Level III-3 study (Kim, 2006)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias	
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias	
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias	
2. Consistency *(If only one study was available, rank this component as 'not applicable')*			
	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*			
The study found that a high INR (≥1.5) is an independent risk factor for FICH in patients with acute leukaemia (RR 3.29; 95% CI 1.25, 8.69). The study also found a trend towards aPTT being an independent risk factor for FICH.	A	Very large	
	B	Substantial	
	C	Moderate	
	D	Slight/Restricted	
	NA	Not applicable/no difference/underpowered	
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
The evidence is generalisable to patients with acute leukaemia	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible	

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Since the study was undertaken at a single site in Korea, the evidence is somewhat applicable to the Australian healthcare context.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	C	Moderate
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.2 In patients with acute leukaemia, INR/PT/APTT levels may be independently associated with mortality.

INR, international normalised ratio; PT, prothrombin time, APTT, activated partial thromboplastin time

Key question(s): In patients with acute leukaemia, what is the association between INR (or PT/APTT) level and the risk of bleeding events?		Evidence Matrix: EM5.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one fair quality Level III-3 study (Dally, 2005)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
The study found that a high PT or aPTT level is not an independent risk factor for severe bleeding in patients with promyelocytic leukaemia.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Since the study population was restricted to patients with acute promyelocytic leukaemia, the evidence is somewhat generalisable to patients with acute leukaemia	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted at a single site in Israel	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

For a rare disease with high mortality, the cohort size is relatively large and well-powered.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.3 In patients with acute promyelocytic leukaemia, the independent association between INR/PT/APTT levels and bleeding events is uncertain.

INR, international normalised ratio; PT, prothrombin time, APTT, activated partial thromboplastin time

Key question(s): In patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy, what is the association between INR (or PT/APTT) level and the risk of mortality?		Evidence Matrix: EM5.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one fair quality Level II study (Nallamothu, 2005). Although this was a multivariate analysis, the authors note that the results may be confounded by greater use of UFH in patients receiving reteplase only.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Nallamothu et al (2005) reported the relative risk of experiencing 30-day mortality in patients who were stratified according to their peak aPTT levels (<50, 50–70, >70 s). The study found that in patients with peak aPTT levels <50 s, increased aPTT levels are associated with a decreased risk of mortality. The relative risk for each one second increase in peak aPTT in patients with peak aPTT <50 seconds was 0.94 (95% CI 0.92, 0.95), when compared with a peak aPTT level of 50 seconds. It should also be noted that the correlations observed are based on peak aPTT levels, and may have been different had aPTT levels been assessed at a specific time point.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This was a large, recent study carried out in a number of sites including Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

This was a large prospective cohort analysis based on RCT data (Nallamothu, 2005). The RCT on which the analysis is based included patients in the first 6 h of evolving ST-segment elevation myocardial infarction who were randomly assigned standard-dose reteplase or half-dose reteplase and full-dose abciximab. Reteplase is an anti-fibrinolytic, and abciximab is an antiplatelet agent. Both study arms were also treated with intravenous unfractionated heparin (UFH). A lower dose of UFH in the combination therapy group was used to compensate for the anticoagulant effect of abciximab.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence directly generalisable to target population with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.4 In heparinised patients with ACS receiving standard-dose reteplase or half-dose reteplase and full-dose abciximab, subtherapeutic peak APTT levels may be associated with an increased risk of mortality.

ACS, acute coronary syndrome; INR, international normalised ratio; PT, prothrombin time, APTT, activated partial thromboplastin time

Key question(s): In patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy, what is the association between INR (or PT/APTT) level and the risk of bleeding?		Evidence Matrix: EM5.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one fair quality Level II study (Nallamothu, 2005). Although this was a multivariate analysis, the authors note that the results may be confounded by greater use of UFH in patients receiving reteplase only.	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Nallamothu et al (2005) reported the relative risk of experiencing 30-day mortality in patients who were stratified according to their peak aPTT levels (<50, 50–70, >70 s). The study found that in patients with peak aPTT levels >70 s, increased aPTT levels are associated with an increased risk of moderate-to-severe bleeding. It should also be noted that the correlations observed are based on peak aPTT levels, and may have been different had aPTT levels been assessed at a specific time point.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The results are generalisable to patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
This was a large, recent study carried out in a number of sites including Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

This was a large prospective cohort analysis based on RCT data (Nallamothu, 2005). The RCT on which the analysis is based included patients in the first 6 h of evolving ST-segment elevation myocardial infarction who were randomly assigned standard-dose reteplase or half-dose reteplase and full-dose abciximab. Reteplase is an anti-fibrinolytic, and abciximab is an antiplatelet agent. Both study arms were also treated with intravenous unfractionated heparin (UFH). A lower dose of UFH in the combination therapy group was used to compensate for the anticoagulant effect of abciximab.

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence directly generalisable to target population with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.5 In heparinised patients with ACS receiving standard-dose reteplase or half-dose reteplase and full-dose abciximab, supratherapeutic peak APTT levels may be associated with an increased risk of moderate-to-severe bleeding.

ACS, acute coronary syndrome; INR, international normalised ratio; PT, prothrombin time, APTT, activated partial thromboplastin time

Key question(s): In patients with liver disease, what is the association between fibrinogen level and the risk of mortality/survival?		Evidence Matrix: EM5.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one poor quality Level II study (Violi, 1995)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
In the study by Violi et al (1995), the fibrinogen level was associated with survival in the univariate analysis but not in the multivariate analysis.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Since the study is in patients with cirrhosis, the results are moderately generalisable to patients with liver disease.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The evidence is somewhat applicable to the Australian healthcare context, although it may now be relatively dated.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.6 In patients with liver disease, an independent association between fibrinogen levels and mortality is uncertain.

Key question(s): In patients with acute leukaemia, what is the association between fibrinogen levels and the risk of mortality?		Evidence Matrix: EM5.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one good quality Level III-3 study (Kim, 2006)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
The study found that in the univariate analysis, serum fibrinogen was not significantly associated with fatal intracranial haemorrhage.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The evidence is generalisable to patients with acute leukaemia	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Since the study was undertaken at a single site in Korea, the evidence is somewhat applicable to the Australian healthcare context; however, the definition of the risk factor differs from that used in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.7 In patients with acute leukaemia, the independent association between fibrinogen levels and mortality is uncertain.

Key question(s): In patients with acute leukaemia, what is the association between fibrinogen levels and the risk of bleeding events?		Evidence Matrix: EM5.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one fair quality Level III-3 study (Dally, 2005)	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
The study found that fibrinogen is not an independent risk factor for bleeding complications in patients with promyelocytic leukaemia.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Since the study population was restricted to patients with acute promyelocytic leukaemia, the evidence is somewhat generalisable to patients with acute leukaemia	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted at a single site in Israel	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

For a relatively rare disease with high mortality, this is a relatively large and well powered cohort.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
1.	Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES5.8 In patients with acute promyelocytic leukaemia, the independent association between fibrinogen levels and bleeding events is uncertain.

Recommendation(s) for prophylactic platelet transfusion in patients undergoing chemotherapy and HSCT

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In patients undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategy for prophylactic use of platelets is transfusion at a platelet count of $<10 \times 10^9$ in the absence of risk factors, and at $<20 \times 10^9$ in the presence of risk factors.	B	EM5.A, EM5.B and EM5.C

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this.* *This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	NO
Are there any resource implications associated with implementing this recommendation?	YES	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
What could help to facilitate implementation of the recommendation?		
Include a requirement to utilise guidelines in the blood and blood product standard. Include in BloodSafe eLearning Include in presentations provided by CRG members at clinical meetings.		

D6 Evidence – Question 6

Key question(s): In patients with thalassaemia, what is the association between pre-transfusion haemoglobin levels and survival?		Evidence Matrix: EM6.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III-2 study Roudbari (2008, fair quality).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
One study only	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
At higher level of pre-transfusion Hb was associated with improved survival. A 1g/dL increase in pre-transfusion Hb was associated with a 33% reduction in the risk of mortality.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered

4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
The included study examined patients with β-thalassaemia.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Roudbari (2008) was conducted in Iran. The results may be applicable to the Australian setting	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

In the Roudbari 2008 study patients lost to follow-up were excluded from analysis and the total number of patients excluded was not reported.

EVIDENCE STATEMENT MATRIX

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

Component		Rating	Description
6.	Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
7.	Consistency	NA	Not applicable (one study only)
8.	Clinical impact	C	Moderate
9.	Generalisability	A	Evidence directly generalisable to target population with some caveats
10.	Applicability	D	Evidence not applicable to Australian healthcare context

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES6.1 In patients with thalassaemia, the effect of the pretransfusion Hb threshold on mortality is uncertain.

Hb, haemoglobin

Key question(s): In patients with thalassaemia, what is the association between pretransfusion haemoglobin levels and transfusion volume?		Evidence Matrix: EM6.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level II studies of poor quality, Masera (1982) and Torcharus (1993), and one Level III-2 study of fair quality, Cazzola (1997).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(If only one study was available, rank this component as 'not applicable')*		
The association between pre-transfusion Hb level and transfusion volume was generally consistent in the three studies. In Masera (1982) the association was only significant in the first five months of treatment.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be*		
Cazzola (1997) reported a significant ($p<0.0001$) association between lower pre-transfusion Hb and lower mean transfusion volume. Torcharus (1993) also reported a lower mean transfusion volume in patients with lower pre-transfusion Hb. Masera (1982) reported a significantly lower ($p<0.01$) mean transfusion volume in patients with lower pre-transfusion Hb in the first 5 months of treatment, but found no significant association after 5 months of treatment.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
All three studies examined patients with either β-thalassaemia or β-thalassaemia and/or HbE. Cazzola (1997) examined patients aged 16 to 30 years while the other two studies examined children (aged 14 years and under).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
Torcharus (1993) was conducted in Thailand while Cazzola (1997) and Masera (1982) were conducted in Italy.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

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

Three subjects were excluded from the Cazzola (1997) study due to death during the moderate transfusion period. Masera (1982) did not report any inclusion or exclusion criteria. In Torcharus (1993) patients treated with hyper-transfusion only and standard transfusion only had different baseline serum ferritin levels (1158 ng/mL vs. 723 ng/mL, respectively).

EVIDENCE STATEMENT MATRIX

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

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

DRAFT EVIDENCE STATEMENT

Based on the body of evidence above.

ES6.2 In patients with thalassaemia, a pretransfusion Hb level of 90–100 g/L may reduce transfusion volume, compared to 100–120 g/L.

Recommendation(s) for haemoglobin thresholds in chronically transfused patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
No recommendation made for this question.		

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

Appendix E Quality analyses

One aspect of the 'strength of the evidence' domain in the NHMRC Dimensions of Evidence is study quality. The full quality checklist developed for Phase II is based on the quality assessment questions that are included in the NHMRC toolkit, *How to use the evidence: assessment and application of scientific evidence* (NHMRC, 2000). Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (eg, good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

Each eligible study was assessed against each quality criterion as Y (yes), N (no), NR (not reported) or NA (not applicable). Where applicable, clarification of the criteria or justification for a downgrading of study quality, were provided as comments. Based on the checklist of quality criteria, studies were ultimately graded as good, fair or poor.

As not all quality assessment criteria are applicable to all study types, separate checklists have been applied for systematic reviews, RCTs and cohort studies.

E1 Quality analysis – Question 1

ACS

Level II evidence

			Study type:	Cohort study	
			Citation:	Anker et al (2009) Prevalence, incidence and prognostic value of anaemia in patients after an acute myocardial infarction: data from the OPTIMAAL trial. European Heart Journal 30: 1331–1339.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
		✓		Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Re-analysis of a double-blind RCT (OPTIMAAL); 91.5% of 5477 randomised patients who had baseline Hb measurement were included in the analysis (no discussion of characteristics of missing patients); results adjusted for a large number of potential confounders including study interventions.	
			Quality rating: [Good/Fair/Poor]	Fair	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Archbold et al (2006) Hemoglobin concentration is an independent determinant of heart failure in acute coronary syndromes: cohort analysis of 2310 patients. Am Heart J 152: 1091–1095.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study based in a cardiac care unit; 2310/3119 (74.1%) had baseline Hb measurements recorded; baseline variables between groups with or without baseline Hb similar with the exception of the proportion of South Asians (34% vs 39%); analysis adjusted for a large number of potential confounders; it is not clear how determination of cardiac death was made and potential for bias due to known Hb status is not addressed; follow-up during hospitalisation.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Aronson et al (2007) Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction. European Heart Journal 28: 1289–1296.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, hospital-based cohort study; 1606 patients willing to participate were identified; 216 excluded due to meeting exclusion criteria (n=194) or missing repeated Hb measurement (n=22); analysis adjusted for a number of potential confounding variables thought to have clinical importance or with P<0.1 in the univariate analysis; mortality ascertained by attempting to contact the patient, reviewing hospital course if rehospitalised, and reviewing national death registry; follow-up median 2 years.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Bassand et al (2010) Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes. European Heart Journal 31: 50–58.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
		✓		Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
		✓		Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of pooled data from two RCTs; no details provided on number of eligible subjects included in analysis but data came from two RCTs so may have been good follow-up and little missing data; analyses adjusted for a variety of potential confounders; all outcome assessment conducted blind to treatment assignment; 30 day follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Burr et al (1992) Haematological prognostic indices after myocardial infarction: evidence from the diet and reinfarction trial (DART). European Heart Journal 13: 166–170.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of a dietary RCT (DART); of 2033 who entered trial, 1877 were seen at the 6 month visit where blood was taken (most of the others died); blood taken from 1755 subjects; no details given on subjects missing from the analysis; analysis adjusted but for very few variables and not those commonly adjusted for in other analyses; 18 months follow-up.	
Quality rating: [Good/Fair/Poor]				Poor	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Cavusoglu et al (2006) Usefulness of anaemia in men as an independent predictor of two-year cardiovascular outcome in patients presenting with acute coronary syndrome. Am J Cardiol 98: 580–584.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, hospital-based cohort study; 193 men eligible, 191 with Hb values, 100% follow-up; analysis adjusted for potential confounders identified by univariate analysis, however race was not included; mortality data obtained by review of Social Security Death Index, medical records, next of kin or primary physician; MI diagnosed using specific troponin values; follow-up 2 years.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Giraldez et al (2009) Baseline haemoglobin concentration and creatinine clearance composite laboratory index improves risk stratification in ST-elevation myocardial infarction. Am Heart J 157: 517–524.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of a 2 prospective RCTs, one used to define a laboratory index and the other to validate it; 14,373/14,799 (97%) included in analysis from the first trial and 18,400/18,427 (99.9%) from the second trial; therefore, some subjects with missing data excluded from the analysis but this was a very small percentage; analysis adjusted for a large number of potential confounding factors; 30 day follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Hasin et al (2009) Prevalence and prognostic significance of transient, persistent and new-onset anemia after acute myocardial infarction. Am J Cardiol 104: 486–491.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Analysis based on data from a prospective hospital-based cohort database; of 1805 discharged from hospital with AMI, 1605 with post-discharge Hb measurement who remained alive after 28 days were included in the analysis; all 1065 included in analysis so assume no loss to follow-up; adjusted for a large number of potential confounders; mortality and heart failure measured via national death registry, patient contact and reviewing hospital course; follow-up mean 27 months (12–44) following post-discharge Hb measurement.	
Quality rating: [Good/Fair/Poor]				Fair	

AMI, acute myocardial infarction; Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Keough-Ryan et al (2005) Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions and anaemia. Am J Kidney Dis 46: 845–855.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of a prospective population-based registry; 6587 had a discharge diagnosis of ACS, 84% (5549) included in analysis – 457 of those excluded died in hospital, 38 had end stage renal disease and 543 had extreme or missing creatinine values; analyses adjusted for a number of confounders but authors note that many other potential confounders not considered due to missing data; outcomes data collected via linkage to Vital Statistics registry; follow-up up to nearly 7 years.	
Quality rating: [Good/Fair/Poor]				Poor	

ACS, acute coronary syndrome.

Study type:				Cohort study	
Citation:				Mahaffey et al (2007) Prediction of one-year survival in high-risk patients with acute coronary syndromes: results from the SYNERGY trial. J Gen Intern Med 23(3): 310–316.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of a RCT; 10,027 enrolled in the study but 9978 available for analysis due to problem with randomisation in 49 patients; complete follow-up available in 99.4% (9922); analysis adjusted for a large number of potential confounders; mortality ascertained via phone, medical records, national death indices or a private locator service (US only); follow-up up to 1 year.	
Quality rating: [Good/Fair/Poor]				Good	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Sabatine et al (2005) Association of haemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 111: 2042–2049.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from 16 RCTs; patients included in analysis were those with baseline haemoglobin data available, no mention of how many were excluded from the analysis; analysis adjusted for a large number of potential confounders which were those in which there was > 80% data availability and that showed an association with baseline Hb (P<0.025) or were known to be of clinical importance; method of outcome data collection not reported; follow-up 30 days.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin; RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Valeur et al (2009) Anaemia is an independent predictor of mortality in patients with left ventricular systolic dysfunction following acute myocardial infarction. European Journal of Heart Failure 8: 577–584.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of RCT data; Hb measurement missing in only 18 of 1749 (1%) of subjects; analysis adjusted for a large number of potential confounders; follow-up 10–12 years.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin; RCT, randomised controlled trial.

Heart failure

Level I/III evidence

Study type	Systematic review	
Citation	Groenveld HF, Januzzi JL, Damman K et al (2008) Anemia and mortality in heart failure patients. A systematic review and meta-analysis. Journal of the American College of Cardiology 52: 818–827.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
Y	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
Y	Was the quality of the studies reported?	III
Y	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Y	Were the characteristics of the individual studies reported?	II-III
N	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Y	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
Y	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
Y	Was a test for heterogeneity applied?	III-IV
Y	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Good quality study with assessment of individual study quality and exploration of heterogeneity and subgroup analysis.*	
Quality rating	*Systematic review: Good*	
	Included studies: Good-Fair	

Study type	Systematic review	
Citation	He S-W, Wang L-W (2009) The impact of anemia on the prognosis of chronic heart failure: a meta-analysis and systematic review. Congestive Heart Failure 15: 123–130.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
Y	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
Y	Was the quality of the studies reported?	III
Y	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Y	Were the characteristics of the individual studies reported?	II-III
Y	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Y	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
Y	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
Y	Was a test for heterogeneity applied?	III-IV
Y	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Good search strategy; limited to prospective observational studies; study quality assessed and 18/20 studies considered to be of high quality; characteristics results of individual studies reported; reported individual study results for adjusted analyses but did not pool results. Some errors found in this publication which have been rectified in the data extraction form but which not have an impact on the interpretation of the results.*	
Quality rating	*Systematic review: Good*	
	Included studies: Good	

Study type	Systematic review	
Citation	Lindenfeld (2005) Prevalence of anemia and effects on mortality in patients with heart failure. Am Heart J 149: 391–401.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
Y	Was more than one database searched?	III
N	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
N	Was the quality of the studies reported?	III
N	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Y	Were the characteristics of the individual studies reported?	II-III
Y	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Y	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
NA	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
NA	Was a test for heterogeneity applied?	III-IV
NA	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Good search strategy; search terms not reported. No quality assessment of individual studies included. Characteristics and results of individual studies reported. No pooling of results.*	
Quality rating	*Systematic review: Fair*	
	Included studies: Poor	

Level II evidence

Study type:				Cohort study	
Citation:				Adams et al (2009) Prospective evaluation of the association between hemoglobin concentration and quality of life in patients with heart failure. American Heart Journal 158: 965–971.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from a prospective registry; two populations analysed – (1) those with baseline data and (2) those with baseline and follow-up data; the characteristics of the patients in these two groups were compared with those with no QoL data at baseline and shown to be similar; assessment of QoL conducted by phone by trained investigators who were unaware of Hb level; follow-up up to 12 months.	
Quality rating: [Good/Fair/Poor]				Good	

Hb, haemoglobin; QoL, quality of life.

Study type:				Cohort study	
Citation:				Anand et al (2005) Anemia and change in haemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation 112: 1121–1127.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Re-analysis of data from a double-blind RCT; a proportion of the patients included in the original RCT (n=5010) not included in re-analysis (may be N=5002 but that is somewhat unclear; reasons for exclusion not stated); mortality is an objective outcome; mean 23 months follow-up; treatment with intervention/control did not affect results (adjusted for in analysis).	
Quality rating: [Good/Fair/Poor]				Fair	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Anker et al (2009) Prevalence, incidence and prognostic value of anaemia in patients after an acute myocardial infarction: data from the OPTIMAAL trial. European Heart Journal 30: 1331–1339.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Re-analysis of a double-blind RCT (OPTIMAAL); 91.5% of 5477 randomised patients who had baseline Hb measurement were included in the analysis (no discussion of characteristics of missing patients); results adjusted for a large number of potential confounders including study interventions.	
Quality rating: [Good/Fair/Poor]				Fair	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Baggish et al (2007) Hemoglobin and N-terminal pro-brain natriuretic peptide: independent and synergistic predictors of mortality in patients with acute heart failure. Results from the International Collaborative of NT-proBNP (ICON) study. Clinica Chimica Acta 381: 145–150.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Combined data from a number of published and unpublished prospective hospital registries; of 720 subjects diagnosed with acute HF, 96% had available haemoglobin data (no details on characteristics of those without Hb measurement); analysis adjusted for a large number of potential confounders; mortality assessed by hospital records, death certificate and telephone follow-up with physician; 60-day follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin; HF, heart failure.

Study type:				Cohort study	
Citation:				Ceresa et al (2005) Anemia in chronic heart failure patients: comparison between invasive and non-invasive prognostic markers. Monaldi Arch Chest Dis 64: 124–133.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
		✓		Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
		✓		If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective hospital-based cohort study; unclear if all available patients included (methods sections states consecutive patients included but discussion notes selected patients); unclear exactly what variables were considered in the multivariate analysis; not stated how follow-up occurred; 3-year follow-up.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Felker et al (2003) Usefulness of anemia as a predictor of death and rehospitalisation in patients with decompensated heart failure. Am J Cardiol 92: 625–628.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Re-analysis of a double-blind RCT; 95% of randomised subjects had baseline Hb measurement and 60-day follow-up was 99%; wide range of variables considered for inclusion in multivariable analysis; mortality a secondary outcome of the RCT.	
Quality rating: [Good/Fair/Poor]				Good	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Garty et al (2007) The management, early and one-year outcome in hospitalized patients with heart failure: a national heart failure survey in Israel – HFSIS 2003. IMAJ 9: 227–233.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective survey of all public hospitals in Israel between March to April 2007 with up to 1 year follow-up of mortality; a large number of risk factors assessed of which anaemia was just one; all subjects included in analyses; adjusted for potential confounders using multivariate analysis; mortality data collected via Israeli registry.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Hamaguchi et al (2009) Anaemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan: a report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circulation Journal 73: 1901–1908.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two or more groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort registry with 2.4 years follow-up; large proportion of potentially eligible subjects not included in analysis (2675 eligible, 1960 had discharge Hb measurement and only 1582 of these followed up; analysis considered a large number of potential confounders; patients surveyed after at least 1 year for outcome status.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Ingle et al (2007) Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. European Heart Journal 28: 560–568.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort from a local community clinic; unclear whether all potentially eligible subjects were included in the analysis; multivariate analysis conducted adjusting for a wide range of variables; no details on how mortality data collected.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Kalra et al (2003) Haemoglobin concentration and prognosis in new cases of heart failure. Lancet 362: 211–212.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study; out of 552 potentially eligible subjects, 531 (96.2%) had haemoglobin values available at presentation and were included in the analysis; analyses were adjusted for a number of potential confounding variables; mortality data collected via notification from the Office of National statistics; follow-up median 3 years.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Komajda et al (2006) The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. European Heart Journal 27:1440–1446.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Re-analysis of the double-blind COMET RCT; only 2.7% (406/14,890) of Hb measurements missing; authors note no interpolation or extrapolation o9f missing values was carried out and patients included as far as the data allowed; adjusted analysis including a large number of potential confounding variables, including randomised treatment; due to multiple testing, p<0.01 considered significant; ~ 5 years follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

Hb, haemoglobin; RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Maggioni et al (2005) Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. Journal of Cardiac Failure 11(2): 91–97.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Data analysed from one prospective registry and one double-blind RCT; consecutive patients included in Registry (no further detail on patients agreeing to take part or loss to follow-up; all 5010 patients from RCT included in analysis; multivariate analysis conducted adjusting for a large number of potential confounding variables; follow-up for 1 and 2 years for RCT and 1 year for Registry.	
Quality rating: [Good/Fair/Poor]				Good	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Maraldi et al (2006) Anemia, physical disability an survival in older patients with heart failure. Journal of Cardiac Failure 12(7): 533–539.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓[a]	✓[b]			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective hospital cohort; no patients had disability at baseline as they were already excluded from the population; of 587 potentially included subjects, 10 excluded as they had dementia or severe cognitive impairment (excluded to avoid potential misclassification of self-report functional status), ten others excluded due to missing Hb concentration; results adjusted for a large number of potential confounders; 12 month follow-up with visits at 6 and 12 months after hospital discharge.	
Quality rating: [Good/Fair/Poor]				Good (mortality)/fair (functional status)	

Hb, haemoglobin.
[a] Mortality.
[b] Disability.

Study type:				Cohort study	
Citation:				Poole-Wilson et al (2003) Mode of death in heart failure: findings from the ATLAS trial. Heart 89: 42–48.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of a double-blind RCT (ATLAS); all randomised subjects included in the analysis – no patients lost to follow up with respect to vital status during the trial; analysis adjusted for a large number of potential confounders; deaths during the trial were adjudicated by a two member endpoint committee; mean follow-up 46 months.	
Quality rating: [Good/Fair/Poor]				Good	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Young et al (2008) Relation of low haemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF Registry). American Journal of Cardiology 101:223–230.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, hospital-based registry; > 48,000 included in registry while 10% (>5,000) were followed for 60–90 days – it is somewhat unclear whether the in-hospital mortality analysis includes the full cohort or subgroup; states that full cohort and subgroup were similar demographically; multivariate analysis includes a large number of potential confounders identified via univariate analysis or previous studies.	
Quality rating: [Good/Fair/Poor]				Fair	

Elderly

Level II evidence

			Study type:	Cohort study	
			Citation:	Chaves et al (2004) What constitutes normal haemoglobin concentration in community-dwelling disabled older women? J Am Geriatr Soc 52: 1811–1816.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Prospective, population-based cohort; 31.5% of eligible subjects did not agree to have blood sample taken (these subjects were older, had more disability and poorer cognitive function so results may underestimate association between Hb and mortality); mortality data obtained for all but 1.7% of subjects; large number of potential confounding variables included in analysis; follow-up median 5 years, maximum 6 years.	
			Quality rating: [Good/Fair/Poor]	Fair	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Denny et al (2006) Impact of anemia on mortality, cognition, and function in community-dwelling elderly. American Journal of Medicine 119: 327–334.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, population-based cohort; 1744 out of initial 2569 subjects had Hb levels measured, of those mortality status was obtained for 1701 after 8 years; analyses adjusted for a number of potential confounding variables; mortality determined by a search of the National Death Index; 8 years follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Dong et al (2008) A population-based study of hemoglobin, race and mortality in elderly persons. Journal of Gerontology 63A(8): 873–878.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, community-based cohort study; residents turning 65 randomly selected at each 3-year study cycle for inclusion; no discussion of subjects who refused to participate; analyses adjusted for a large number of potential confounding factors; outcome measured via informants, newspaper obituaries and verified through matching with the National death Index; mean 3.9 year follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Endres et al (2009) Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. Current Medical Research and Opinion 25(5): 1143–1158.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, primary care-based cohort; 344 family physicians recruited 6880 patients, only 4 lost to follow-up; analyses adjusted for a large number of potential confounding factors; mortality collected by case-report forms submitted by clinicians or by consulting records kept by residency registration offices; maximum 5.3 years follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Izaks et al (1999) The definition of anemia in older persons. JAMA 281(18): 1714–1717.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, community-based cohort study; 75% of the eligible population included in the analysis; the analysis adjusted for a number of factors, but these are done in separate analyses; mortality data was gathered from death certificates obtained from the civic registries; follow-up was 10 years.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Lucca et al (2008) Association of mild anemia with cognitive, functional, mood and quality of life outcomes in the elderly: the "Health and Anemia" study. PLoS ONE 3(4): e1920. Doi: 10.1371/journal.pone.0001920.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cross-sectional study; of 10,110 potentially eligible residents, 4501 agreed to take part and accepted the blood tests and health questionnaire (those who refused were slightly older [1 year]; of those, 4068 were then considered eligible (265 anaemia and 4157 anaemia); 170/265 anaemia residents had mild anaemia and completed the blood tests and interview while 547/4068 non-anaemia residents were randomised and completed the blood tests and interview; residents included and excluded were compared and the only differences were less women taking part (8.7%), more with a history of MI (1.8%) and more educated (0.5 years); the two latter variable are thought to be associated with the difference in women; the analysis was adjusted for a large number of potential confounding and a number of sensitivity analyses were undertaken including for disease severity, cancer and renal disease; interviews conducted by nurses and psychologists with high agreement between them (Cohen's κ 0.84–0.93).	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Patel et al (2007) Racial variation in the relationship of anemia with mortality and mobility disability among older adults. Blood 109: 4663–4670.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, community-based cohort study; 3075 initially recruited, Hb assessment occurred at the second year of follow-up and included 2601 participants; those not included were older, more likely to self-identify as black and had more medical conditions (ie, may have been at greater risk of mortality); only 2574 included in analysis – no details regarding this are provided; analysis adjusted for a large number of potential confounding factors; mortality assessed every six months by telephone contact and confirmed with death certificate; mobility difficulty defined as two consecutive reports of having a lot of difficulty or not being able to walk a quarter mile or up 10 steps without resting; follow-up up to 6 years.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Patel et al (2009) Haemoglobin concentration and the risk of death in older adults: differences by race/ethnicity in the NHANES III follow-up. British Journal of Haematology 145: 514–523.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, population-based cohort; of 5252 potentially eligible subjects, 4199 had haemoglobin values available for analysis and of those 4090 identified as one of the three racial groups under consideration; in one additional patient vital status could not be determined; therefore there were 4089 subjects available for analysis; the authors note that those with missing haemoglobin values were older, more likely to be female, and less likely to be Mexican-American than non-Hispanic white and more likely to die during follow-up; analyses adjusted for a large number of potential confounders; follow-up 12 years.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Penninx et al (2006) Anemia in old age is associated with increased mortality and hospitalization. Journal of Gerontology 61A(5): 484–479.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, community-based cohort study; only 3607 were included in the analysis due to lack of blood collection at baseline (visit 6 over overarching cohort study); no details provided on subjects who did not have blood collected; analysis adjusted for variables shown to be (borderline) associated with anaemia in univariate analyses; mortality data collected via proxies, obituaries in local newspapers and the National Death Index; mean 4.1 years follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Riva et al (2009) Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anemia population-based study. Haematologica 94(1): 22–28.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, population-based cohort study; of 10,110 residents in Biella, Italy, 4,501 agreed to participate; however, Hb data were available for an additional 3,035 individuals so analyses were conducted on two population: (i) participants and (ii) non-participants with available Hb data; analysis of participants conducted using different models including different confounders; analysis of participant an non-participant data adjusted for only age and sex; up to 3.5 years follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Thien et al (2009) Diminished quality of life and physical function in community-dwelling elderly with anemia. Medicine (Baltimore) 88(2): 107–114.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Cross-sectional survey with prospective collection of Hb and functional/performance status data and retrospective collection of potential confounding variable data; five subjects with missing Hb data excluded from analysis (no details of patients provided); analysis adjusted for a number of known potential confounders; no details on collection of data in terms of trained personnel or blinding of Hb status.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Zakai et al (2005) A prospective study of anaemia status, haemoglobin concentration and mortality in an elderly cohort. Archives of Internal Medicine 165: 2214–2220.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, community-based cohort study; of those screened, 9.6% were ineligible to participate and 57.3% of those eligible enrolled; of 5888 participants, 5797 had baseline haemoglobin determined (98.5%); no discussion of characteristics of those who did not enrol is included; analysis adjusted for a number of confounders; follow-up a mean of 11.2 years.	
Quality rating: [Good/Fair/Poor]				Fair	

Cancer

Level I/III evidence

Study type	Systematic review	
Citation	Caro JJ, Salas M, Ward A, Goss G (2001) Anemia as an independent prognostic factor for survival in patients with cancer. Cancer 91: 2214–2221.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
N	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
N	Was the quality of the studies reported?	III
N	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
N	Were the characteristics of the individual studies reported?	II-III
N	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
N	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
Y	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
N	Was a test for heterogeneity applied?	III-IV
N	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Reasonable search strategy but only Medline searched. No quality assessment of individual studies included. No characteristics of individual studies reported. Likely heterogeneity noted but not assessed.*	
Quality rating	*Systematic review: Poor*	
	Included studies: Poor	

Study type	Systematic review	
Citation	Hauser CA, Stockler MR, Tattersall MHN (2006) Prognostic factors in patients with recently diagnosed incurable cancer: a systematic review. Support Care Cancer 14:999–1011.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
N	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
NR	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
N	Was the quality of the studies reported?	III
N	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
N	Were the characteristics of the individual studies reported?	II-III
N	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
N	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
NA	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
NA	Was a test for heterogeneity applied?	III-IV
NA	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Reasonable search strategy but only Medline searched. No quality assessment of individual studies included. No characteristics of individual studies reported. No individual results reported. No pooling of results. Describes only the number of studies which showed a significant association between anaemia and survival time using univariate and multivariate analyses.*	
Quality rating	*Systematic review: Poor*	
	Included studies: Poor	

Study type	Systematic review	
Citation	Knight K, Wade S, Balducci L (2004) Prevalence and outcomes of anemia in cancer: a systematic review of the evidence. Am J Med 116 (7A): 11S-26S.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
Y	Was more than one database searched?	III
N	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Unknown	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
N	Was the quality of the studies reported?	III
N	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Y	Were the characteristics of the individual studies reported?	II-III
N	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
N (only qualitatively)	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
NA	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
NA	Was a test for heterogeneity applied?	III-IV
NA	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Search strategy not fully described (ie, no search terms reported) ; type of studies to be included not defined a priori; study quality not assessed; characteristics of individual studies reported; only qualitative descriptions of results of individual studies. No pooling of results.*	
Quality rating	*Systematic review: Poor*	
	Included studies: Poor	

Study type	Systematic review	
Citation	Kramer AH, Zygun DA (2009) Anemia and red blood cell transfusion in neurocritical care. Critical Care 13: R89 (doi: 10.1186/cc7916).	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
N	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
N	Were inclusion/exclusion criteria reported?	II
Unclear	Was the inclusion criteria applied in an unbiased way?	III
Unclear	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
N	Was the quality of the studies reported?	III
N	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Y	Were the characteristics of the individual studies reported?	II-III
N	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Y	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
NA	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
NA	Was a test for heterogeneity applied?	III-IV
NA	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Reasonable search strategy but only Medline searched. No inclusion/exclusion criteria specified. No quality assessment of individual studies included. Only some of the included studies relevant to this review. Individual study results briefly described. No pooling of results.*	
Quality rating	*Systematic review: Poor*	
	Included studies: Poor	

Level II evidence

			Study type:	Cohort study	
			Citation:	Armstrong et al (2010) Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clinical Cancer Research 16(1): 203–211.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Prospective, hospital-based cohort analysis of a RCT; of 1006 men who took part in the RCT, 789 men completed 10 cycles of chemotherapy or progressed while on treatment; of the 789 men eligible, an additional 149 were excluded from the analysis due to missing data; men excluded did differ compared with men included in the analysis; a large number of potential confounders were considered in the multivariate analysis and only those which were significant (P<0.1) were retained in the model; follow-up was sufficient as at time of analysis, 82% of subjects had died and median survival was 14.5 months.	
			Quality rating: [Good/Fair/Poor]	Good	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Beer et al (2006) The prognostic value of haemoglobin change after initiating androgen-deprivation therapy for newly diagnosed metastatic prostate cancer: a multivariate analysis of Southwest Oncology Group Study 8894. Cancer 107: 489–496.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, hospital-based cohort analysis of a RCT; of 1286 registered subjects, 827 were eligible had data available for all analysed variables; of these, an additional 10 were excluded as they dies or progressed within 3 months of registration; survival and progression-free survival were similar between those included and excluded from the analysis; adjusted for a number of potential confounding variables; follow-up at least 2 years.	
Quality rating: [Good/Fair/Poor]				Good	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Cook et al (2006) Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clinical Cancer Research 12(11): 3361–3367.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort analysis of a hospital-based RCT; 592/643 potentially eligible subjects with a complete dataset were included; no comment made on any differences between the included and excluded subjects; a large number of potential confounding variables examined; follow-up up to 2 years.	
Quality rating: [Good/Fair/Poor]				Fair	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Halabi et al (2009) Progression-free survival as a predictor of overall survival in men with castrate-resistant prostate cancer. Journal of Clinical Oncology 27(17): 2766–2771.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from 9 RCTs; Data from 1296 men available but only 1201 included in analysis; no explanation given for missing subjects; analysis adjusted for a number of variables known to be prognostic for survival; ascertainment of survival status not described; follow-up not stated but given median survival shown to be up to 17.8 months in one of the subgroups, is likely to have been sufficient for this population and outcome.	
Quality rating: [Good/Fair/Poor]				Poor	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Köhne et al (2002) Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Annals of Oncology 13: 308–317.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
		✓		Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort analysis of a large number of hospital-based RCTs and phase II studies; no details provided on how many subjects from each trial included in the analysis although the paper does state that 30% had missing Hb data and missing data for other variables ranged from 0% to 72%; the analysis appears to have been adjusted for a number of variables although it is unclear exactly what these were; it is unclear how long follow-up was.	
Quality rating: [Good/Fair/Poor]				Poor	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Laurie et al (2007) The impact of anaemia on outcome of chemoradiation for limited small-cell lung cancer: a combined analysis of studies of the National Cancer Institute of Canada Clinical Trials Group. Annals of Oncology 18: 1051–1055.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
		✓		Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort analysis of data from two hospital-based RCTs; all 652 subjects included in the baseline Hb analysis; the nadir Hb analysis included 633/652 subjects while the pre-PCI Hb analysis included 523/652 subjects; no comparison of patients included or excluded from the analyses is provided; a number of variables were examined for inclusion in the adjusted analysis and only 4 including Hb remained; length of follow-up is unclear.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin; PCI, prophylactic cranial irradiation; RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Mandrekar (2006) A prognostic model for advanced stage nonsmall cell lung cancer: pooled analysis of North Central Cancer Treatment Group trials. Cancer 107: 781–792.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort analysis of pooled data from nine RCTs; 1053 subjects available for analysis; only 782 of these included in the multivariate analysis; no details provided on the comparison between included and excluded subjects; results adjusted for a number of potential confounders although the authors note that there may have been many others not included due to different data collection in different trials; follow-up appears to be at least 2 years.	
Quality rating: [Good/Fair/Poor]				Poor	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Négrier et al (2002) Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Français d'Immunothérapie. Annals of Oncology 13: 1460–1468.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from five prospective trials; no details provided on patients included in/excluded from analysis, although there is a note that there was a limited number of missing values and that the highest was 13% for inflammation markers; analysis adjusted for 15 variables identified during univariate analysis; follow up median 77 months.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Nieboer et al (2005) Fatigue and relating factors in high-risk breast cancer patients treated with adjuvant standard or high-dose chemotherapy: a longitudinal study. Journal of Clinical Oncology 23(33): 8296–8304.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
		✓		If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cross-sectional/longitudinal cohort analysis of data from a RCT; of 838 potentially eligible, 804 completed one or more QoL questionnaires; at 3 years follow-up 430 were available and disease-free; only 426 available for analysis of Hb at baseline and < 300 by year 3; adjusted for a number of potential confounders but a number of other known confounders have not been assessed; outcome assessment subjective and unclear if patients aware of haemoglobin status so potential for bias.	
Quality rating: [Good/Fair/Poor]				Poor	

Hb, haemoglobin; QoL, quality of life; RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Østerlind et al (1986) Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Research 46: 4189–4194.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of six RCTs; 874 subjects included in trials, up to 778 included in analysis; no details of why subjects were missing from the analysis is reported; no details on included subjects is provided; analyses adjusted for variables shown to have significant influence; follow-up 2 years.	
Quality rating: [Good/Fair/Poor]				Poor	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Paesmans et al (1995) Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European Lung Cancer Working Party. Journal of Clinical Oncology 13: 1221–1230.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from 7 RCTs; 5.6% of subjects lost to follow-up; a large number of potential confounding variables considered in the analysis; analysis adjusted for variables shown to be significant in the stepwise regression analysis; follow-up median 270 weeks.	
Quality rating: [Good/Fair/Poor]				Fair	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Paesmans et al (2000) Prognostic factors for patients with small-cell lung cancer: analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. Cancer 89: 523–533.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from 4 RCTs; no details provided on patients who may have been excluded from the analysis; 21 potential confounding variables examined, with 4 included in the best-fit model, median follow-up 118 months.	
Quality rating: [Good/Fair/Poor]				Fair	

RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Wisløff et al (2005) Quality of life may be affected more by disease parameters and response to therapy than by haemoglobin changes. European Journal of Haematology 75: 293–298.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
				Was follow-up long enough for outcomes to occur?	III
Comments:				Cross-sectional cohort analysis of data from two prospective trials; 521/583 (89%) in study 1 and 224/284 (79%) in study 2 completed the questionnaire at baseline and follow-up; no discussion of the characteristics of those who did not participate in the QoL study; analysis adjusted for a large number of potential confounding variables; subjective outcome and unclear if subjects or investigators were aware of the Hb status so potential for bias.	
Quality rating: [Good/Fair/Poor]				Poor	

Hb, haemoglobin; QoL, quality of life.

Renal

Level I/III evidence

			Study type:	Systematic review	
			Citation:	Volkova et al (2006) Evidence-based systematic literature review of hemoglobin/haematocrit and all-cause mortality in dialysis patients. American Journal of Kidney Diseases 47(1): 24–36.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
	✓			Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
	✓			Was the quality of the studies reported?	III
	✓			Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
	✓			Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
			✓	If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
			✓	Was a test for heterogeneity applied?	III-IV
			✓	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
			Comments:	*Good literature search; no hand-searching reported but checked search results against an existing review; no formal assessment of study quality but some studies were excluded due to poor methodology; data not pooled.*	
			Quality rating: [Good/Fair/Poor]	Systematic review: Fair	
				Included studies: Not reported	

Level II evidence

			Study type:	Cohort study	
			Citation:	Abramson et al (2003) Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: The ARIC Study. Kidney International 64: 610–615.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
		✓		Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Data taken from a large prospective cohort study; analysis includes 87% of the 15,792 participants included at baseline; no details provided on how many declined to participate or loss to follow-up; not stated if outcome assessment blind to CKD/anaemia status; 9 years follow-up.	
			Quality rating: [Good/Fair/Poor]	Fair	

CKD, chronic kidney disease.

Study type:				Cohort study	
Citation:				Astor et al (2006) Kidney function and anaemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. American heart Journal 151: 492–500.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Data taken from a large prospective cohort study; analysis includes 95% of the 15,792 participants included at baseline; 65–67% of eligible participants in three centres and 46% in another centre completed the baseline examination; not stated if outcome assessment blind to GFR/anaemia status; 12 years follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

GFR, glomerular filtration rate.

Study type:				Cohort study	
Citation:				Avram et al (2003) Hemoglobin predicts long-term survival in dialysis patients: a 15-year single-center longitudinal study and a correlation trend between prealbumin and hemoglobin. Kidney International 64 (Supplement 87): S6-S11.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
			✓	Was outcome assessment blinded to exposure status?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, single-centre, hospital-based cohort study; does not state if any patients refused participation; all patients followed up; no adjustment for co-morbidities, other than for diabetes in the continuous analysis; follow-up up to 16 years (mean 4 years).	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study/cross-sectional analysis	
Citation:				Finkelstein et al (2009) Health-related quality of life and hemoglobin levels in chronic kidney disease patients. Clin J Am Soc Nephrol 4: 33–38.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Cross-sectional analysis of data from a prospective cohort study (CRIOS); 2295 patients enrolled from 7 centres in US and Canada; 1186 completed the QoL questionnaires; only data collected within 60 days of QoL assessment included in analysis (numbers not provided); subjects who completed the QoL assessment were similar to those who did not with the exception of age and % men; analysis adjusted for a number of confounders including ESA use; subjective outcome, unclear if subjects aware of Hb status when completing QoL assessment.	
Quality rating: [Good/Fair/Poor]				Fair	

ESA, erythropoiesis stimulating agent; Hb, haemoglobin; QoL, quality of life; US, United States of America.

Study type:				Cohort study	
Citation:				Fort et al (2010) Mortality in incident haemodialysis patients: time-dependent haemoglobin levels and erythropoiesis-stimulating agent dose are independent predictive factors in the ANSWER study. Nephrol Dial Transplant 25: 2702–2710.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective hospital-based cohort study; 62.5% of dialysis facilities agreed to participate; baseline characteristics are reported for 2341 patients which it is reported makes up ~58% of all incident dialysis patients during the study period; 2310 were ultimately included in the study (no reason for the reduced number is given); follow up was up to 2 years (mean 1.5 years).	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Leeder et al (2005) Low hemoglobin, chronic kidney disease, and risk for coronary heart disease-related deaths: the Blue Mountains Eye Study. J Am Soc Nephrol 17: 279–284.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective, community-based cohort study; 580 (15.9%) excluded due to missing or incomplete data; those excluded were similar to the included population except for having more pre-existing CHD and higher rates of CHD deaths; adjusted for a number of potential confounding factors; mean 8.2 years follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

CHD, chronic heart disease.

			Study type:	Cohort study	
			Citation:	Merkus et al (1997) Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. American journal of Kidney Diseases 29(4): 584–592.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
			Comments:	Cross-sectional study; of 250 available for the study, 226 (90.4%) completes the SF-36; those who did not complete it either didn't speak Dutch well enough and/or could not read and fill out the questionnaire themselves; those who did not complete the SF-36 were more likely to be male, and have a lower Hb; analysis adjusted for a number of confounders based on univariate analysis and stepwise selection; unclear if patients aware of Hb status (subjective outcome).	
			Quality rating: [Good/Fair/Poor]	Fair	

Hb, haemoglobin; SF-36, Short Form (36) Health Survey.

Study type:				Cohort study	
Citation:				Mollaoglu (2004) Depression and health-related quality of life in hemodialysis patients. Dialysis and Transplantation 33(9): 544–579.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Cross-sectional study; 140/150 eligible patients completed the SF-36 and BDI (no details of excluded subjects provided); only adjusted for a small number of potential confounders; subjective outcome – unclear if subjects aware of Hb status.	
Quality rating: [Good/Fair/Poor]				Poor	

BDI, Beck Depression Inventory; Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Perlman et al (2005) Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the renal research institute–CKD study. American journal of Kidney Diseases 45(4): 659–666.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Cross-sectional study; overall cohort (N=634) mean age 60.7 years, male 56%, Caucasian 75%; SF-36 population (N=505) mean age 60.2, male 58%, Caucasian 77%; 487 with Hb measurement. Differences between those completing and not completing the SF-36 included % Caucasian (77% vs 66%), diabetes (35% vs 45%) and college education (66% vs 45%); authors note they did not detect bias; analysis adjusted for a number of confounders; subjective outcome (unclear if Hb status known).	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin; SF-36, Short Form (36) Health Survey.

Study type:				Cohort study	
Citation:				Plantinga et al (2007) Relation between level or change of hemoglobin and generic and disease-specific quality of life measures in hemodialysis. Qual Life Res 16: 755–765.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study with both cross-sectional and longitudinal analyses; 767 patients available; 313 did not have 1-year QoL and 16 did not have 6-month Hb; authors state that those missing from analysis were similar to those included; analyses adjusted for a few potential confounders, these chosen based on analyses or known association with QoL; subjective outcomes, unclear if measured without awareness of anaemia status.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin; QoL, quality of life.

Study type:				Cohort study	
Citation:				Portolés et al (2007) A prospective multicentre study of the role of anaemia as a risk factor in haemodialysis patients: the MAR study. Nephrol Dial Transplant 22: 500–507.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study; Used two-stage cluster sampling to identify a sample making up > 8% of prevalent patients in 2000; of 1710 in sample, 1428 completed follow-up (no details provided on patients who were not included in analysis); analysis adjusted for a number of potential confounders; follow-up 1 year.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Robinson et al (2005) Anemia and mortality in hemodialysis patients: accounting for morbidity and treatment variables updated over time. Kidney International 68: 2323–2330.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
			✓	Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study; of 7300 who took part in the US DOPPS study, 7104 had one of more Hb values, 6167/5517/4610 were eligible for the 1/3/6 month lagged models; checked analysis to test if included subjects representative of the eligible subjects and they were; adjusted for a large number of potential confounders including EPO; performed analyses to check for median follow-up for 3 month lagged model 13.4 months.	
Quality rating: [Good/Fair/Poor]				Fair	

EPO, erythropoietin; Hb, haemoglobin; US, United States of America.

			Study type:	Cohort study	
			Citation:	Stevens et al (2004) Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol 15: 770–779.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Prospective hospital-based cohort study; 515 had complete data, no indication of how many excluded from analysis or what their characteristics were; 97 patients censored during the study due to transplant (N=88) or lost to follow-up (N=9); analysis adjusted for a number of known confounders as well as mineral metabolism markers; follow-up up to 3 years (median 32 months).	
			Quality rating: [Good/Fair/Poor]	Fair	

Study type:				Cohort study	
Citation:				Türk et al (2004) Quality of life in male hemodialysis patients. Nephron Clin Prac 96:c21-c27.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Cross-sectional analysis of data from a prospective cohort study; of 511 haemodialysis patients, 148 male patients meeting the criteria were included (no details provided on male patients who did not meet criteria); variables found to be significant in univariate analysis considered in multivariate analysis; subjective outcome, unclear if patients aware of Hb status.	
Quality rating: [Good/Fair/Poor]				Poor	

Hb, haemoglobin.

Study type:				Cohort study	
Citation:				Yen et al (2010) Association between body mass and mortality in maintenance hemodialysis patients. Therapeutic Apheresis and Dialysis 14(4): 400–408.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study; 959 included (no information of excluded subjects or those refusing to participate); adjusted for a number of variables that remained significant in stepwise analysis (excluded Hb as a variable); 3 year follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin

E2 Quality analysis – Question 2

Mixed/General population

Level I evidence

Study type	Systematic review	
Citation	Carless et al (2010) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD002042. DOI: 10.1002/14651858.CD002042.pub2.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
Y	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
Y	Was the quality of the studies reported?	III
Y	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Y	Were the characteristics of the individual studies reported?	II-III
Y	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Y	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
Y	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
Y	Was a test for heterogeneity applied?	III-IV
Y	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Thorough literature search conducted; included RCTs only; quality of studies assessed; individual study results reported; meta-analysis conducted including all studies; heterogeneity assessed and discussed.*	
Quality rating	*Good*	

ACS

Level III evidence

			Study type:	Cohort study	
			Citation:	Alexander et al (2008) Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. American Heart Journal 155: 1047–1053.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Retrospective cohort study; 72% of potentially eligible subjects included in analysis; no consideration of potential differences between included and excluded population; analysis adjusted for a large number of potential confounders; in-hospital follow-up.	
			Quality rating: [Good/Fair/Poor]	Fair	

Study type:				Cohort study	
Citation:				Rao et al (2004) Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 282: 1555–1562.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
		✓		Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
		✓		Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from three RCTs so unlikely to be substantial follow-up bias; analysis performed in three ways and adjusted for a large number of potential confounding variables; mortality measured over short time period.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Sabatine et al (2005) Association of haemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 111: 2042–2049.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from 16 RCTs; patients included in analysis were those with baseline haemoglobin data available, no mention of how many were excluded from the analysis; analysis adjusted for a large number of potential confounders which were those in which there was > 80% data availability and that showed an association with baseline Hb (P<0.025) or were known to be of clinical importance; method of outcome data collection not reported; follow-up 30 days.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin; RCT, randomised controlled trial.

Study type:				Cohort study	
Citation:				Shishehbor et al (2009) Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2:46–53.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
		✓		Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
		✓		Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Cohort analysis of data from a RCT; of the 4131 subjects with STEMI in the trial, 53 were excluded for missing transfusion data and 503 who were part of a CABG study were excluded; analysis adjusted for a large number of potential confounding variables; follow-up up to 1 year.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Wu et al (2001) Blood transfusion in elderly patients with acute myocardial infarction. New England Journal of Medicine 345(17): 1230–1236.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Retrospective hospital-based cohort; cohort taken from a larger Medicare-based study cohort; of 234,769 subjects, 17,593 excluded for being < 65 years, 45,349 for not having confirmed AMI, 23,773 for being readmitted for MI; 81,306 excluded for being transferred to or from the study hospital; other reasons for exclusion included co-morbidities, high or implausible Hct levels; in total 33.6% of the original cohort were included in the study; analysis adjusted for a large number of potential confounders, many of which were identified via univariate and stepwise analyses; follow-up 30 days.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Yang et al (2005) The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes. Journal of the American College of Cardiology 46(8): 1490–1495.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Retrospective hospital-based cohort study; population taken from the CRUSADE study from Jan 2001 to Mar 2004; of the 98,571 eligible, 74,271 had complete transfusion data, had not undergone CABG while hospitalised and had not been transferred to another hospital; analysis adjusted for a large number of potential confounders although Hct doesn't appear to have been included; follow-up while in hospital.	
Quality rating: [Good/Fair/Poor]				Poor	

Heart Failure

Level III evidence

Study type:				Cohort study	
Citation:				Garty et al (2009) Blood transfusion for acute decompensated heart failure – friend or for? American heart Journal 158: 653–658.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective nationwide hospital-based survey; of 4102 HF subjects, 2335 had ADHF and were included; outcome was determined in 99% of patients in first 12 months; outcome measured via database or by cross-referencing with the Israel National Population Death Register; up to 4 years follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Cancer

Level III evidence

Study type:				Cohort study	
Citation:				Khorana et al (2008) Blood transfusions, thrombosis and mortality in hospitalised patients with cancer. Archives of Internal Medicine 168(21): 2377–2381.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Retrospective hospital-based cohort study with disease, intervention and outcome data collected via ICD-9 codes; measures taken to reduce bias caused by this including excluding sites with under or inconsistent reporting of transfusion, and excluding subjects with a primary diagnosis of VTE or ATE; regression analysis used to identify potential confounders; follow-up while in hospital.	
Quality rating: [Good/Fair/Poor]				Fair	

Acute Gastrointestinal Haemorrhage

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Blair et al (1986) Effect of early blood transfusion on gastrointestinal haemorrhage. British Journal of Surgery 73: 783–785.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			Was loss to follow-up reported?	II
		✓		Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				Randomised but no method stated; not double-blind but objective outcome (mortality); appears to be no loss to follow-up; ITT analysis carried out; 5/26 patients randomised to no transfusion in 24 hours arm received transfusion due to Hb < 8 g/dL; study underpowered to detect a difference in mortality.	
Quality rating: [Good/Fair/Poor]				Poor	

Level III evidence

Study type:				Cohort study	
Citation:				Hearnshaw et al (2010) Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding. Alimentary Pharmacology and Therapeutics 32: 215–224.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Hospital-based cohort study; 212/257 (82%) of hospitals participated; of 8939 potential submitted cases, 1199 did not meet exclusion criteria, 1190 had insufficient data, 5004 underwent endoscopy and 4441 had complete info on RBC transfusion; the authors note there were no important differences in demographic characteristics between those included and those excluded due to incomplete data; analysis adjusted for Rockall Score and baseline Hb; 30-day follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

E3 Quality analysis – Question 3

Cancer

Level I evidence

Study type:				Systematic review	
Citation:				Tonelli M, Lloyd A, Lee H, Wiebe N, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Klarenbach S. (2009) Erythropoiesis-stimulating agents for anemia of cancer or of chemotherapy: systematic review and economic evaluation [Technology report number 119]. Ottawa: Canadian Agency for Drugs and Technologies in Health.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
	✓			Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: > 5 good quality studies	

Study type:				Systematic review	
Citation:				Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke MJ, Weingart O, Kluge S, Piper M, Napoli M, Rades D, Steensma D, Djulbegovic B, Fey MF, Ray-Coquard I,Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Engert A. (2009) Erythropoietin or Darbepoetin for patients with cancer - meta-analysis based on individual patient data. Cochrane Database of systematic reviews. Issue 3. Art. No.: CD007303. DOI: 10.1002/14651858.CD007303.pub2 .	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: At least 10 studies were considered good quality	

Level II evidence

			Study type:	Randomised controlled trial	
			Citation:	Christodoulou C, Dafni U, Aravantinos G, Koutras A, Samantas E, Karina M, Janinis J, Papakostas P, Skarlos D, Kalofonos HP, Fountzilas G (2009) Effects of epoetin-(alpha) on quality of life of cancer patients with solid tumors receiving chemotherapy. Anticancer Res 29(2):693–702.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
	✓			Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
	✓			Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
			Comments:	The study was an open label RCT with a primary outcome of QOL. The open-label nature of the trial may have affected the QOL results. The analysis of the primary outcome of QOL was poor (not a correct ITT or PP analysis) and did not allow any of the data for QOL to be extracted.	
			Quality rating: [Good/Fair/Poor]	Poor	

Study type:				Randomised controlled trial	
Citation:				Hernandez E, Ganly P, Charu V, DiBenedetto J, Tomita D, Lilliee T, Taylor K (2009) Randomized, double-blind, placebo-controlled trial of every-3-week darbepoetin alfa 300 micrograms for treatment of chemotherapy-induced anemia. Curr Med Res Opin 25(9):2109–20.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				Method of analysis for transfusion incidence was unusual. Reporting of randomisation and allocation concealment was poor. The study reported a high incidence of important protocol violations.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Hoskin PJ, Robinson M, Slevin N, Morgan D, Harrington K, Gaffney C (2009) Effect of epoetin alfa on survival and cancer treatment-related anemia and fatigue in patients receiving radical radiotherapy with curative intent for head and neck cancer. J Clin Oncol 27(34):5751–6.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
				Were subgroup analyses reported?	III-IV
				Were subgroup analyses appropriate?	III-IV
Comments:				An open label RCT examining survival and QoL.Possible bias in QoL reporting due to open label status. Patients may not be considered anaemic at baseline	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Randomised controlled trial	
Citation:				Pronzato P, Cortesi E, van der Rijt CC, Bols A, Moreno-Nogueira JA, de Oliveira CF, Barrett-Lee P, Ostler PJ, Rosso R (2010) Epoetin alfa improves anemia and anemia-related, patient-reported outcomes in patients with breast cancer receiving myelotoxic chemotherapy: Results of a european, multicenter, randomized, controlled trial. Oncologist 15(9):935–43.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
			✓	Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
		✓		Were subgroup analyses appropriate?	III-IV
Comments:				An open label RCT. Randomisation method not reported. Possibility for bias in the reporting of QOL outcomes with the open label design.	
Quality rating: [Good/Fair/Poor]				Fair	

QoL, quality of life; RCT, randomised controlled trial.

Study type:				Randomised controlled trial	
Citation:				Tsuboi M, Ezaki K, Tobinai K, Ohashi Y, Saijo N (2009) Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: Results of a multicenter, phase III, randomized, double-blind, placebo-controlled study. Jpn J Clin Oncol 39(3):163–8.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:				The method of treatment allocation was not reported. The method for dealing with missing data in QoL analysis led to an overestimation of the effect. Consequently the per protocol data has been extracted.	
Quality rating: [Good/Fair/Poor]				Fair	

QoL, quality of life.

Study type:				Randomised controlled trial	
Citation:				Auerbach M, Silberstein PT, Webb T, Averyanova S, Ciuleanu T-E, Shao J, Bridges K. (2010) Darbepoetin alfa 300 or 500 μg once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. American Journal of Haemotology 85:655–663.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Randomised controlled trial	
Citation:				Bastit L, Vandebroek A, Altintas S, Gaede B, Pintet T, Suto TS, Mossman TW, Smith KE, Vansteenkiste JF. (2008) Randomized, Multicenter, Controlled Trial Comparing the Efficacy and Safety of Darbepoetin Alfa Administered Every 3 Weeks With or Without Intravenous Iron in Patients With Chemotherapy-Induced Anemia. Journal of Clinical Oncology 26(10): 1611–8.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				Transfusions were performed at investigator discretion and were recommended, but not required, for patients with Hb ≤8.0 g/dL or patients with Hb more than 8 g/dL if they exhibited anaemia symptoms.	
Quality rating: [Good/Fair/Poor]				Fair	

Hb, haemoglobin.

Study type:				Randomised controlled trial	
Citation:				Dangsuwan P, Manchana T. (2010) Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy. Gynecologic oncology 116:522–5.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Hedenus M, Birgegard G, Nasman P, Ahlberg L, Karlsson T, Lauri B, Lundin J, Larfars G, Osterborg A (2007) Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia 21: 627–32.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Randomised controlled trial	
Citation:				Pedrazzoli P, Farris A, Del Prete S, Del Gaizo F, Ferrari D, Bianchessi C, Colucci G, Desogus A, Gamucci T, Pappalardo A, Fornarini G, Pozzi P, Fabi A, Labianca R, Di Costanzo F, Secondino S, Crucitta E, Apolloni F, Del Santo A, and Siena S. (2008) Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alfa. Journal of Clinical Oncology 26(10):1615–25.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Fair	

Chronic heart failure

Level I evidence

			Study type:	Systematic review	
			Citation:	Desai A, Lewis E, Solomon S, McMurray JJV, and Pfeffer M. (2010) Impact of erythropoiesis-stimulating agents on morbidity and mortality in patients with heart failure: An updated, post-TREAT meta-analysis. European Journal of Heart Failure 12:936–942.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
	✓			Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
			Comments:		
			Quality rating: [Good/Fair/Poor]	Systematic review: Good	
				Included studies:	

Study type:				Systematic review	
Citation:				Jin B, Luo X, Lin H, Li J, and Shi H. (2010) A meta-analysis of erythropoiesis-stimulating agents in anaemic patients with chronic heart failure. European Journal of Heart Failure 12:249–253.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies:	

Study type:				Systematic review	
Citation:				Lawler PR, Filion KB, and Eisenberg MJ. (2010) Correcting anemia in heart failure: The efficacy and safety of erythropoiesis-stimulating agents. Journal of Cardiac Failure 16:649–658.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
	✓			Was a test for heterogeneity applied?	III-IV
			✓	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Fair Included studies:	

Study type:				Systematic review	
Citation:				Ngo K, Kotecha D, Walters JAE, Palazzuoli A, van Veldhuisen DJ, Flather M. (2010) Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD007613. DOI: 10.1002/14651858.CD007613.pub2.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				Adequate generation of the randomisation sequence was found in six studies. In general, concealment of allocation was poorly reported but was judged to be adequate in five studies including 77% of the study participants (n=616). Blinding was variable: five studies were double-blinded, three studies had only outcome assessors blinded, two studies did not adequately report methods and one study was not blinded. Out of the 11 studies, only two studies were not placebo-controlled (Silverberg 2001, Cosyns 2008). Regarding incomplete outcome data, most of the studies were short term so the loss to follow-up was low. Withdrawals and associated reasons were reported in five studies. There was limited evidence of selective outcome reporting. The four studies that were judged to be inadequate in this domain had not specified their primary outcomes and one study did not specify the follow-up period, which ranged from 5 to 12 months (Silverberg 2001). Another potential source of bias was imbalance in baseline characteristics between groups. In one study, the ESA group had more diabetics and less use of beta-blockers than control (van Veldhuisen 2007). In another study, the ESA group had greater distance on the 6MWT at baseline (405m versus 321m) (Mancini 2003). However it was difficult to assess the similarity of study groups at baseline as most studies did not include tests for statistical significance of baseline differences. The type of publication also influenced quality of outcome reporting. Ten studies were published as full text papers in print journals and one study was published as a letter to the editor (Cosyns 2008).	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Good quality: Ghali 2008, Ponikowski 2007, van Veldhuisen 2007, Fair: Kourea 2008a, Parissis 2008, Palazzuoli 2006, Palazzuoli 2007	

	Poor quality: Cleland 2005, Cosyns 2008, Mancini 2003, Silverberg 2001	

6-minute walk test; ESA, erythropoiesis stimulating agent.

Study type:				Systematic review	
Citation:				Tehrani F, Dhesi P, Daneshvar D, Phan A, Rafique A, Siegel RJ, and Cercek B. (2009) Erythropoiesis stimulating agents in heart failure patients with anemia: A meta-analysis. Cardiovascular Drugs and Therapy 23:511–518.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
	✓			Was the quality of the studies reported?	III
			✓	Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies:	

Study type:				Systematic review	
Citation:				Van Der Meer P, Groenveld HF, Januzzi J, and van Veldhuisen DJ. (2009) Erythropoietin treatment in patients with chronic heart failure: A meta-analysis. Heart 95:1309–1314.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓	✓			Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓	✓			Was a test for heterogeneity applied?	III-IV
✓	✓			If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				Did not report individual (or heterogeneity) data for outcomes other than mortality and CHF-related hospitalisation	III
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies:	

CHF, chronic heart failure.

Level II evidence

				Study type:	Randomised controlled trial
				Citation:	Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Luscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, Eisenhart Rothe BE, Pocock SJ, Poole-Wilson PA, and Ponikowski P. (2009) Ferric carboxymaltose in patients with heart failure and iron deficiency. New England Journal of Medicine 361:2436–2448.
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
				Comments:	Because ferric carboxymaltonse is a dark-brown solution that is easily distinguishable from the saline placebo, study personnel responsible for the preparation and administration of the study drug were aware of group assignments and therefore were not involved in any study assessments. To ensure that patients were unaware of the study drug they were receiving, black syringes were used to administer the study treatment and a curtain was used to shield the injection site from the patient's view.
				Quality rating: [Good/Fair/Poor]	Good

Study type:				Randomised controlled trial	
Citation:				Okonko DO, Grzeslo A, Witkowski T, Mandal AKJ, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, and Ponikowski P. (2008) Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency. FERRIC-HF: A Randomized, Controlled, Observer-Blinded Trial. Journal of the American College of Cardiology 51:103–112.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation? Investigators were blinded but not the patients.	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Poor	

Chronic kidney disease

Level I evidence

Study type:				Systematic review	
Citation:				Gandra SR, Finkelstein FO, Bennett AV, Lewis EF, Brazg T, Martin ML. (2010) Impact of erythropoiesis-stimulating agents on energy and physical function in nondialysis CKD patients with anemia: a systematic review. Am J Kidney Dis 55:519–534.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
	✓			Was the quality of the studies reported?	III
			✓	Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
	✓			Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
			✓	If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
			✓	Was a test for heterogeneity applied?	III-IV
			✓	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				Failed to identify relevant RCTs	
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: NR	

NR, not reported; RCT, randomised controlled trial.

Study type:				Systematic review	
Citation:				Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C, Mayne TJ. (2010) Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis 55:535–548.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
		✓		Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
	✓			Was the quality of the studies reported?	III
			✓	Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
		✓		Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: NR	

NR, not reported.

Study type:				Systematic review	
Citation:				Tonelli M, Lloyd A, Lee H, Wiebe N, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Klarenbach S. (2009) Erythropoiesis-stimulating agents for anemia of cancer or of chemotherapy: systematic review and economic evaluation [Technology report number 119]. Ottawa: Canadian Agency for Drugs and Technologies in Health.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
	✓			Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: > 5 good quality studies	

Study type:				Systematic review	
Citation:				Cody JD, Daly C, Campbell MK, Khan I, Rabindranath KS, Vale L, Wallace SA, Macleod AM, Grant A, Pennington S. (2005) Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. Cochrane Database of Systematic Reviews Issure 3. Art. No.: CD003266. DOI: 10.1002/14651858.CD003266.pub2.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
	✓			Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
✓				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				Potential bias at trial entry Fifteen of the studies stated that the order of treatment had been randomly allocated. In twelve trials the method of random allocation was not described. Three studies (Lim 1989; Teplan 2003: Watson 1989) described a secure method of random allocation concealment prior to final trial entry (third party involvement). In correspondence with Teplan (Teplan 2003) we were informed that sealed envelopes were used to allocate participants to treatment. Potential bias at time of treatment or outcome assessment Eight of the studies were double blind, explicitly stating patients and health care providers were blinded to treatment status. Six of these eight described an effective method of 'blinding'. Two gave no description. Two studies explicitly stated there was no 'blinding' of patient and health care providers (Clyne 1992; Roth 1994) Of the eight studies which were 'double blind' there was no specific mention of outcome blinding. In correspondence with Teplan (Teplan 2003), whilst carrying out the first update of the review, we were informed that participants, investigators and outcome assessors were blinded and that sealed envelopes were used to allocate patients to groups, however there is no mention of this in the published paper. Potential for bias in trial analysis Five studies (Clyne 1992; Kleinman 1989; Kuriyama 1997; Lim 1989; Roth 1994) mentioned the numbers and reasons for withdrawals or dropouts. One study (Abraham 1990) performed an intention-to-treat analysis.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Good	

Study type:				Systematic review	
Citation:				Rozen-Zvi B, Gafter-Gvili A, Paul M, Leibovici L, Shpilberg O, Gafter U. (2008) Intravenous versus Oral Supplementation for the Treatment of Anemia in CKD: Systematic Review and Meta-analysis. American Journal of Kidney Disease. 52: 897–906	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
	✓			Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
	✓			If appropriate, was a meta-analysis conducted? Selection criteria for mortality outcome different to what we are looking for in GQ3	III-IV
				F. Were the sources of heterogeneity explored?	
✓				Was a test for heterogeneity applied?	III-IV
✓				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				Note: They included RCTs comparing IV vs Oral in HD and PD-CKD according to KDOQI guidelines. Not by level of anaemia. Authors cite limitations in: Heterogeneity of basal/change in Hb levels, ESA use/dosage/titration Short-term follow up Incidence of severe adverse events unknown Subgroups, such a pre-dialysis, who may benefit from IV treatment	
Quality rating:				Systematic review: Fair	

[Good/Fair/Poor]	Included studies: Studies of interest to GQ3 highlighted in *italics* <u>CKD patients</u> *Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A (2006) A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. Am J Nephrol 26:445–454* Aggarwal HK, Nand N, Singh S, Singh M, Hemant, Kaushik G (2003) Comparison of oral versus intravenous iron therapy in predialysis patients of chronic renal failure receiving recombinant human erythropoietin. *J Assoc Physicians India* 51:170–174 Charytan C, Qunibi W, Bailie GR(2005) Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract* 100:c55-c62 Spinowitz BS, Besarab A, Bolton WK, et al (2006) Ferumoxytol as an intravenous iron replacement therapy in chronic kidney disease (CKD) patients not on dialysis—Evaluation of safety and efficacy in two phase III studies. *J Am Soc Nephrol* 17:342A (Meeting abstract) *Stoves J, Inglis H, Newstead CG (2001). A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. Nephrol Dial Transplant 16:967–974* *Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S (2005) A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. Kidney Int 68:2846–2856* <u>CKD + dialysis patients</u> Allegra V, Mengozzi G, Vasile A (1991) Iron deficiency in maintenance hemodialysis patients: Assessment of diagnosis criteria and of three different iron treatments. *Nephron* 57:175–182 *Fishbane S, Frei GL, Maesaka J (1995) Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. Am J Kidney Dis 26:41–46* Li H, Wang SX (2008) Intravenous iron sucrose in Chinese hemodialysis patients with renal anemia. *Blood Purif* 26:151–156 Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE (1996) A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 50:1694–1699 Michael B, Trout JR, Horl WH, Volinn W, Jorjensen N, Dahl NV (2007) Effectiveness of continuous low-dose intrave-nous ferric gluconate therapy for maintaining Hb and decreasing epoetin requirement in hemodialysis patients. *JAm Soc Nephrol* 18:289A. (Meeting abstract) Svara F, Sulkova S, Kvasnicka J, Polakovic V (1996)[Iron supplementation during erythropoietin therapy in patients on hemodialysis]. *Vnitr Lek* 42:849–852 Warady BA, Kausz A, Lerner G, et al (2004) Iron therapy in the pediatric hemodialysis population. *Pediatr Nephrol* 19:655–661	

Level II evidence

			Study type:	Randomised controlled trial	
			Citation:	Pfeffer MA, Burdmann EA, Chen C-Y, Cooper ME, Zeeuw D, Eckardt K-U, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJV, Parfrey P, Parving H-H, Remuzzi G, Singh AK, Solomon SD, Toto R. (2009) A trial of dardepoetin alfa in Type 2 diabetes and chronic kidney disease. New Eng J Med. 361(21):2019–2032.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
				Comments:	A third party used a point-of-care device to monitor hemoglobin levels and enter the value into an interactive voice-response system that selected the dosage according to a computer algorithm (see the Supplementary Appendix). This algorithm was designed to adjust the dose in order to maintain the hemoglobin level at approximately 13.0 g per deciliter in the patients assigned to darbepoetin alfa. Patients in the placebo group were assigned to receive darbepoetin alfa as a rescue agent if the hemoglobin level fell below 9.0 g per deciliter, with a return to placebo once the hemoglobin level was 9.0 g per deciliter or higher. The site investigator was to be notified if any patient had a hemoglobin value of 7.0 g per deciliter or less, a value of 16.0 g per deciliter or more, or a decrease of 2.0 g per deciliter or more in a 4-week period.
				Quality rating: [Good/Fair/Poor]	Good

Study type:				Randomised controlled trial	
Citation:				Cianciaruso B; Ravani P, Barrett BJ, Levin A. (2008) Italian randomized trial of hemoglobin maintenance to prevent or delay left ventricular hypertrophy in chronic kidney disease. J Nephrol. 21: 861–870.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				• Was the use of randomisation reported?	I
✓				• Was the method of randomisation reported?	III
✓				• Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				• Was a method of allocation concealment reported?	III
✓				• Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			• Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				• Were baseline patient characteristics and demographics reported?	III
✓				• Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				• Was loss to follow-up reported?	II
✓				• Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				• Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓e				• Was outcome assessment blinded to treatment allocation?	IV
✓e				• If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				• Were the methods used for comparing results between treatment arms appropriate?	III
✓				• If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	• Were subgroup analyses reported?	III-IV
			✓	• Were subgroup analyses appropriate?	III-IV
Comments:				Allocation concealment using sealed opaque envelopes.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Randomised controlled trial	
Citation:				Macdougall IC, Temple RM, Kwan TC. (2007) Is early treatment of anaemia with epoetin-α beneficial to pre-dialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomized, comparative group trial. Nephrol Dial Transplant 22: 784–793.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting	

				subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A (2006) A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *Am J Nephrol* 26:445–454.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
	✓			Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? Self-assessed KDQoL	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				18.2 % (N=8) of patients in the treatment arm were excluded from the mITT population because of a lack of post baseline Hb value: Inclusion violation (N=3), Laboratory handling/processing errors (N=4), started ESA/blood transfusion prior to obtaining a post baseline Hgb (N=1). 13.3 % (N=6) of patients in the control arm were excluded from the mITT population because of a lack of post baseline Hb value; all from inclusion violation (N= 6).	
Quality rating: [Good/Fair/Poor]				Fair	

ESA, erythropoiesis stimulating agent; Hb, haemoglobin; mITT, modified intention to treat

Study type:				Randomised controlled trial	
Citation:				Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, and Pereira BJG. (2009) Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clinical Journal of the American Society of Nephrology* 4:386–393.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate? 1:1 randomisation of patients to IV or oral iron group using a telephone-based system. Is it appropriate? (p.387)	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
		✓		Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate? Not to mortality outcome	III-IV
Comments:				"The BP pattern after ferumoxytol was virtually identical to that among patients treated with oral iron in the randomized phase."	
Quality rating: [Good/Fair/Poor]				Fair	

BP, blood pressure; IV, intravenous.

Study type:				Randomised controlled trial	
Citation:				Stoves J, Inglis H, Newstead CG (2001). A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. Nephrol Dial Transplant 16:967–974	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				Patients were assessed by a clinician each month. A 3-day diary of food intake and subjective visual analogue score of GI symptoms were recorded. There was a loss to follow-up of 29%. There is a discrepancy between the diagram showing loss to follow-up and number of patients in the PP population.	
Quality rating: [Good/Fair/Poor]				Poor	

GI, gastrointestinal.

Study type:				Randomised controlled trial	
Citation:				Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S (2005) A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 68:2846–2856	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
		✓		If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				16.8 % (N = 16) of patients in the treatment arm were excluded from the mITT population because of: unstable ESA dose prior to randomisation (N=8), lack of baseline efficacy data (N =4) or were discontinued prior to dosing (N =4). 11.8 % (N = 11) of patients in the treatment arm were excluded from the mITT population because of: unstable ESA dose prior to randomisation (N=8), lack of baseline efficacy data (N =1) or were discontinued prior to dosing (N =2). The use of a transfusion protocol was not reported.	
Quality rating: [Good/Fair/Poor]				Poor	

Abbreviations:ESA, erythropoiesis stimulating agent; mITT, modified intention to treat.

Study type:				Randomised controlled trial	
Citation:				Singh H, Reed J, Noble S, Cangiano J, van Wyck D. (2006) Effect of Intravenous Iron Sucrose in Peritoneal Dialysis Patients who Receive Erythropoiesis-Stimulating Agents for Anemia: A Randomized, Controlled Trial. Clinical Journal of the American Society of Nephrology.1(3): 475–482	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
	✓			Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
		✓		Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
	✓			Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				Randomisation conducted after enrolment (patient screening for eligibility). Mexican study sites were permitted to enrol subjects with lower Hb limits because of the severity of anemia. The authors conclude that they found no overall country effect or selective country effect on Hb outcomes when comparing Mexican and US study patients. Open-label. Without blinding outcomes and IV iron dosage would have been dependent on the investigators assessment. An anaemia management intervention protocol was provided. 17.5% (N=14) of patients in the treatment arm were excluded from the ITT population because of unstable ESA dose prior to randomisation (N=9) or were discontinued prior to dosing (N=5) 35% (N=16) of patients in the control arm were excluded from the ITT population because of unstable ESA dose prior to randomisation (N=8) or lack of baseline efficacy data (N=8)	
Quality rating: [Good/Fair/Poor]				Poor	

ESA, erythropoiesis stimulating agent; Hb, haemoglobin; ITT, intention to treat; IV, intravenous.

Elderly

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Agnihotri P, Telfer M, Butt Z, Jella A, Cella D, Kozma CM, Ahuja M, Riaz S, and Akamah J. (2007) Chronic anemia and fatigue in elderly patients: Results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa. Journal of the American Geriatrics Society 55:1557–1565.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
			✓	If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				Approx. 13% loss to follow-up. Analysis was not conducted ITT. But reasons for loss to follow-up were reported.	
Quality rating: [Good/Fair/Poor]				Fair	

ITT, intention to treat.

Hepatitis C

Level II evidence

			Study type:	Randomised controlled trial	
			Citation:	Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, and Bowers PJ. (2004) Epoetin Alfa Maintains Ribavirin Dose in HCV-Infected Patients: A Prospective, Double-Blind, Randomized Controlled Study. Gastroenterology 126:1302–1311.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
			Comments:	Each eligible patient was assigned a patient number in strict sequential order according to the patient number on the study drug container. To maintain the blind, the study drug container had a 2-part, tear-off label with directions for use and other information on each part. The tear-off section of the label contained a concealed area identifying the study drug (epoetin alfa or placebo) and was removed and attached to the patient's case report form when the drug was administered. The second part of the label contained all identifying information except for the identity of the drug. Study drugs were identical in appearance and were packaged in identical containers.	
			Quality rating: [Good/Fair/Poor]	Fair	

Study type:				Randomised controlled trial	
Citation:				Dieterich DT, Wasserman R, Brau N, Hassanein TI, Bini EJ, Bowers PJ, and Sulkowski MS. (2003) Once-Weekly Epoetin Alfa Improves Anemia and Facilitates Maintenance of Ribavirin Dosing in Hepatitis C Virus-Infected Patients Receiving Ribavirin Plus Interferon Alfa. American Journal of Gastroenterology 98:2491–2499.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Poor	

HIV or AIDS

Level I evidence

Study type:				Systematic review	
Citation:				Marti-Carvajal AJ and Sola I. (2007) Treatment for anemia in people with AIDS. Cochrane Database of Systematic Reviews.	
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
✓				Were the databases searched reported?	III
✓				Was more than one database searched?	III
✓				Were search terms reported?	IV
✓				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
✓				Were inclusion/exclusion criteria reported?	II
✓				Was the inclusion criteria applied in an unbiased way?	III
✓				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
✓				Was the quality of the studies reported?	III
✓				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
✓				Were the characteristics of the individual studies reported?	III
✓				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
✓				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
	✓			If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
	✓			Was a test for heterogeneity applied?	III-IV
	✓			If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:				The authors did not perform meta-analyses due to the differences in populations and outcomes across the studies.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Fair (Fischl 1990, Rendo 2001), Poor (Sulkowski 2005)	

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Fischl M, Galpin JE, Levine JD, Groopman JE, Henry DH, Kennedy P, Miles S, Robbins W, Starrett B, Zalusky R, Abels RI, Tsai HC, Rudnick SA (1990). Recombinant human erythropoietin for patients with AIDS treated with zidovudine. The New England Journal of Medicine 322:1488–93.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				No transfusion protocol reported.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Sulkowski MS, Dieterich DT, Bini EJ, Brau N, Alvarez D, DeJesus E et al. (2005). Epoetin alfa once weekly improves anemia in HIV/Hepatitis C virus-coinfected patients treated with interferon/ribavirin: a randomized controlled trial 39:504–6.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Poor	

Inflammatory bowel disease

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Kulnigg S, Stoinov S, Simanenkov V, Dudar L, Karnafel W, Garcia LC, Sambuelli AM, D'Haens G, Gasche C. (2008) A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT®) randomized controlled trial. American Journal of Gastroenterology 103:1182–92.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
	✓			Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				The quality of life outcome is subject to bias due to the lack of blinding.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Schroder O, Mickisch O, Seidler U, de Weerth A, Dignass AU, Herfarth H, Reinshagen M, Schreiber S, Junge U, Schrott M, Stein J. (2005) Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease–a randomized, controlled, open-label, multicentre study. American Journal of Gastroenterology 100:2503–2509.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
	✓			Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
	✓			Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				24% loss to follow-up. There was an imbalance between study arms in the baseline proportion with Crohn's or ulcerative colitis.	
Quality rating: [Good/Fair/Poor]				Poor	

Myelodysplastic syndrome

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Greenberg, P. L. et al., 2009, Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: Results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996): Blood, v. 114, no. 12, p. 2393–2400.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
		✓		Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
		✓		Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:				Paper did not report blinding at all. Description of loss of follow-up: "118 patients with MDS enrolled into the study. However, information on 8 patients was unevaluable because of insufficient data. Thus, 110 patients enrolled through ECOG institutions were included in this study." It is not clear from this description whether the 8 patients not included in the analysis were randomised to treatment arms.	
Quality rating: [Good/Fair/Poor]				Poor	

ECOG, Eastern Cooperative Oncology Group; MDS, myledysplastic syndrome.

Study type:				Randomised controlled trial	
Citation:				Thompson JA, Gilliland DG, Prchal JT, Bennett JM, Larholt K, Nelson RA, Rose EH, and Dugan MH. (2000) Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. Blood 95:1175–1179.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
	✓			If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				Transfusion protocol NR.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Randomised controlled trial	
Citation:				Ferrini PR, Grossi A, Vannucchi AM, Barosi G, Guarnone R, Piva N, Musto P, and Balleari E. (1998) A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. British Journal of Haematology 103:1070–1074.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
			✓	Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				More information on baseline characteristics could have been provided, including haemoglobin concentration, prior RBC transfusion, and serum erythropoietin concentration. Safety analysis population NR.	
Quality rating: [Good/Fair/Poor]				Poor	

NR, not reported; RBC, red blood cell.

E4 Quality analysis – Question 4

Fresh frozen plasma

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Leese, T., M. Holliday, D. Heath, A. W. Hall, and P. R. F. Bell, 1987, Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis: British Journal of Surgery, v. 74, no. 10, p. 907–911.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
		✓		Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				This was a relatively large, well-designed study. Difficulties in blinding were likely to be due to the nature of the intervention.	
Quality rating:				Fair	

Study type:				Randomised controlled trial	
Citation:				Leese, T., M. Holliday, M. Watkins, J. P. Neoptolemos, W. M. Thomas, A. Attard, and C. Hall, 1991, A multicentre controlled clinical trial of high-volume fresh frozen plasma therapy in prognostically severe acute pancreatitis: Annals of the Royal College of Surgeons of England, v. 73, no. 4, p. 207–214.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
✓				Was loss to follow-up reported?	II
		✓		Was loss to follow-up appropriately accounted for in the analysis?	III-IV
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				This was a relatively large, well-designed study. Difficulties in blinding were likely to be due to the nature of the intervention.	
Quality rating:				Fair	

Study type:				Randomised controlled trial	
Citation:				Gazzard, B. G., R. Clark, V. Borirakchanyavat, and R. Williams, 1974, A controlled trial of heparin therapy in the coagulation defect of paracetamol-induced hepatic necrosis: Gut, v. 15, p. 89–93.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
		✓		Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				The small size of the study was not optimal to detect any clinically or statistically significant differences in clinical outcomes between the two groups. Many details about randomisation, allocation of concealment and analysis were not reported.	
Quality rating: [Good/Fair/Poor]				Poor	

Prophylactic platelet transfusion

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Solomon J, Bofenkamp T, Fahey JL, Chillar RK, Beutler E, et al. Platelet prophylaxis in acute non-lymphoblastic leukemia. The Lancet 1978;1 (8058):267	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
	✓			Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
	✓			Were baseline patient characteristics and demographics reported?	III
			✓	Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
	✓			Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				Poor quality study of limited applicability given changes in chemotherapy since it was undertaken.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Randomised controlled trial	
Citation:				Higby DJ, Cohen E, Holland JF, Sinks L. The prophylactic treatment of thrombocytopenic leukemic patients with platelets: a double blind study. Transfusion 1974;14:440–445	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
	✓			Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
		✓		Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
	✓			Were baseline patient characteristics and demographics reported?	III
			✓	Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				Small poor quality study of questionable applicability to current clinical practice.	
Quality rating: [Good/Fair/Poor]				Poor	

Level III-IV evidence

Study type:				Cohort study	
Citation:				Khorana et al (2008) Blood transfusions, thrombosis and mortality in hospitalised patients with cancer. Archives of Internal Medicine 168(21): 2377–2381.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Retrospective hospital-based cohort study with disease, intervention and outcome data collected via ICD-9 codes; measures taken to reduce bias caused by this including excluding sites with under or inconsistent reporting of transfusion, and excluding subjects with a primary diagnosis of VTE or ATE; regression analysis used to identify potential confounders; follow-up while in hospital.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Case series	
Citation:				Slichter, S. J., 1997, Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions: New England Journal of Medicine, v. 337, no. 26, p. 1861–1869.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Where the case series collected in more than one centre	III-IV
✓				Are the inclusion and exclusion criteria clearly reported	II
✓				Is there an explicit statement that patients were recruited consecutively?	III
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Are outcomes stratified?	II
✓				Were confounding factors reported consistently and prospectively?	II-III
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	II-III
✓				Were all outcomes reported prospectively?	
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Results based on the combined outcomes from both treatment arms of an RCT (comparing photochemically treated with conventional platelets). The incidence of transfusion-related adverse events were not stratified by risk factors.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Case series	
Citation:				McCullough 2004	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Where the case series collected in more than one centre	III-IV
✓				Are the inclusion and exclusion criteria clearly reported	II
✓				Is there an explicit statement that patients were recruited consecutively?	III
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Are outcomes stratified?	II
✓				Were confounding factors reported consistently and prospectively?	II-III
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	II-III
✓				Were all outcomes reported prospectively?	
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				Results based on the combined outcomes from both treatment arms of an RCT (comparing photochemically treated with conventional platelets). Platelet transfusion were given according to each institutions guidelines either prophylacticially to prevent bleeding or therapeutically to treat existing bleeding or prepare for an invasive procedure.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Case series	
Citation:				Heim 2008	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
	✓			Where the case series collected in more than one centre	III-IV
✓				Are the inclusion and exclusion criteria clearly reported	II
✓				Is there an explicit statement that patients were recruited consecutively?	III
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Are outcomes stratified?	II-IV
✓				Were confounding factors reported consistently and prospectively?	II-III
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	II-III
✓				Were all outcomes reported prospectively?	
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				A standardized questionnaire was introduced in 1997 and attached to each PLT product from the apheresis laboratory of the University hospital asking for information about patient factors and transfusion results. The former included weight and height, diagnosis, main treatment, and the presence or absence of fever at the time of transfusion. The latter asked for PLT counts before transfusion (pretransfusion count) and 15 to 60 minutes after transfusion (postransfusion count). Transfusions were given between 2 and 6 hours after measuring the pretransfusion PLT counts. In addition, side effects occurring during or after transfusion of the PLT product were noted.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Case series	
Citation:				Osselaer 2008	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Where the case series collected in more than one centre	III-IV
✓				Are the inclusion and exclusion criteria clearly reported	II
✓				Is there an explicit statement that patients were recruited consecutively?	III
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Are outcomes stratified?	II
✓				Were confounding factors reported consistently and prospectively?	II-III
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	II-III
✓				Were all outcomes reported prospectively?	
				E. Was follow-up adequate?	
			✓	Was follow-up long enough for outcomes to occur?	III
Comments:				There was the potential for overreporting due to the absence of a blinded design and the increased awareness among observers that a new type of PLT component was under evaluation. This was partly addressed: at one of the study centres, the researchers compared the prevalence of transfusion associated adverse events rates in this case series with the prospective data collected during an 18-month period before routine implementation of PLT components treated with pathogen inactivation. The researchers found a significant reduction in reactions to treated platelet components, while the incidence of reactions to RBCs was equal in both periods. This suggests that observer sensitivity for overreporting did not occur.	
Quality rating: [Good/Fair/Poor]				Poor	

Platelet dose

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Slichter, S. J. et al., 2010, Dose of prophylactic platelet transfusions and prevention of hemorrhage: New England Journal of Medicine, v. 362, no. 7, p. 600–613.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
✓				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:				It should be noted that the population was not restricted to adults; however the baseline demographics suggest that the majority of patients were adults.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Randomised controlled trial	
Citation:				Heddle, N. M. et al., 2009, A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia: Blood, v. 113, no. 7, p. 1564–1573.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				A pre-established safety threshold indicated that the study should be stopped by the DSMB if the cumulative incidence of Grade 4 bleeding exceeded an absolute difference of 5% between the two study arms at any time after 50 patients had been enrolled into each treatment arm. The DSMB stopped the study in March 2008, based on this stopping rule, after enrollment of a total of 130 patients.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Randomised controlled trial	
Citation:				Tinmouth A, Tannock IF, Crump M, et al. Low-dose prophylactic platelet transfusions in recipients of an autologous peripheral blood progenitor cell transplant and patients with acute leukemia: a randomized controlled trial with a sequential Bayesian design. Transfusion 2004; 44: 1711–9.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:				The study involved a non-traditional Bayesian design. The study was limited by the fact that investigators were not blinded to treatment and the lack of data on the number of platelets transfused.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Goodnough LT, Kuter DJ, McCullough J, et al. Prophylactic platelet transfusions from healthy apheresis platelet donors undergoing treatment with thrombopoietin. Blood 2001; 98: 1346–51.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
	✓			Was loss to follow-up reported?	II
			✓	Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
			✓	Were subgroup analyses appropriate?	III-IV
Comments:				Patients were assigned to different treatments on a “first-in, first-out basis”. It is unclear if this is an appropriate method of randomisation.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Sensebé L, Giraudeau B, Bardiaux L, et al. The efficiency of transfusing high doses of platelets in hematologic patients with thrombocytopenia: results of a prospective, randomized, open, blinded end point (PROBE) study. Blood 2005; 105:862–4.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
			✓	Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
	✓			Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:				There was no blinding of subjects. Study included patients with acute leukaemia and autologous transplant patients, however the numbers of each group were small and probably underpowered.	
Quality rating: [Good/Fair/Poor]				Poor	

E5 Quality analysis – Question 5

Platelet count and prophylactic platelet transfusion

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Rebulla, P., G. Finazzi, F. Marangoni, G. Avvisati, L. Gugliotta, G. Tognoni, T. Barbui, F. Mandelli, and G. Sirchia, 1997, The threshold for prophylactic platelet transfusion in adults with acute myeloid leukemia: New England Journal of Medicine, v. 337, no. 26, p. 1870–1875.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
✓				Was a method of allocation concealment reported?	III
✓				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
✓				Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
		✓		If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
	✓			Were subgroup analyses appropriate?	III-IV
Comments:				Therapeutic transfusions for bleeding were allowed in both arms, independently of platelet count, but details of the definition of a therapeutic transfusion were not provided. Very few protocol violations compared with other studies of platelet triggers.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Randomised controlled trial	
Citation:				Heckman, K. D., G. J. Weiner, C. S. Davis, R. G. Strauss, M. P. Jones, and C. P. Burns, 1997, Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000/(mu)L versus 20,000/(mu)L: Journal of Clinical Oncology, v. 15, no. 3, p. 1143–1149.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
✓				Was the method of randomisation reported?	III
✓				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
			✓	Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:				What constituted a life-threatening bleed was an issue of potential importance given the lack of blinding. No patient in either group died from haemorrhage or underwent major surgery as a result of bleeding complications, meaning that the study was underpowered to detect differences in these outcomes.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Diedrich, B., M. Remberger, A. Shanwell, B. M. Svahn, and O. Ringden, 2005, A prospective randomized trial of a prophylactic platelet transfusionOKA trigger of 10 null 109 per L versus 30 null 109 per L in allogeneic hematopoietic progenitor cell transplant recipients: Transfusion, v. 45, no. 7, p. 1064–1072.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
✓				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
✓				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
	✓			Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
Comments:				Generally a well-designed, adequately powered study.	
Quality rating: [Good/Fair/Poor]				Fair	

			Study type:	Randomised controlled trial	
			Citation:	Zumberg, M. S., M. L. del-Rosario, C. F. Nejame, B. H. Pollock, L. Garzarella, K. J. Kao, R. Lottenberg, and J. R. Wingard, 2002, A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplant recipients: 10,000/L versus 20,000/microL trigger: Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, v. 8, p. 569–576.	
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
	✓			Was the method of randomisation reported?	III
		✓		Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
	✓			Was a method of allocation concealment reported?	III
		✓		Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
	✓			Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
✓				Were baseline patient characteristics and demographics reported?	III
	✓			Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
✓				Was loss to follow-up reported?	II
✓				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to treatment allocation?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
✓				Were the methods used for comparing results between treatment arms appropriate?	III
			✓	If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
✓				Were subgroup analyses reported?	III-IV
✓				Were subgroup analyses appropriate?	III-IV
			Comments:	The mean platelet count in patients with a trigger of 20 x 10^9/L was higher at baseline than it was for the group of patients with a trigger of 20 x 10^9/L. It was not reported if this differences was significant. It should also be noted that 49% of the transfusions in the lower trigger arm and 21% of transfusions in the higher trigger arm were given above the assigned trigger level.	
			Quality rating: [Good/Fair/Poor]	Poor	

Different INR (or PT/aPTT) levels

Study type:				Prospective cohort study	
Citation:				Garden OJ, Motyl, H, Gilmour WH, Utley RJ and Carter DC (1985) Prediction of outcome following acute variceal haemorrhage. British Journal of Surgery 72: 91–95	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
	✓			Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				It should also be noted that the study did not stratify patients by different prothrombin time thresholds, but rather reported the association between absolute prothrombin ratio and admission mortality.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Prospective cohort study	
Citation:				Violi, 1995	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
	✓			Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective population based cohort with relatively long follow-up period.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Nallamothu, B. K. et al., 2005, Prognostic implication of activated partial thromboplastin time after reteplase or half-dose reteplase plus abciximab: Results from the GUSTO-V trial: European Heart Journal, v. 26, no. 15, p. 1506–1512.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Large prospective cohort analysis based on RCT data. The combination therapy group had a higher percentage of patients with hypertension and hyperlipidaemia, but other characteristics including age, gender, median body mass index (BMI), and weight were similar across both groups. Peak aPTT values were higher (median, 87.3 vs. 66.0 s; P = 0.001) and more rapidly reached (median, 7.2 vs. 19.3 h; P = 0.001) in patients receiving standard-dose reteplase compared with combination therapy. Confounding due to heparin treatment was not adjusted for.	
Quality rating: [Good/Fair/Poor]				Fair	

Level III evidence

			Study type:	Retrospective cohort study	
			Citation:	Le Moine, O. et al., 1992, Factors related to early mortality in cirrhotic patients bleeding from varices and treated by urgent sclerotherapy: Gut, v. 33, no. 10, p. 1381–1385.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Retrospective cohort study. Relatively dated so may not be applicable to current standard practice. With only 102 patients, it may also be underpowered to accurately estimate the association between measured parameters and death.	
			Quality rating: [Good/Fair/Poor]	Good	

Study type:				Retrospective cohort study	
Citation:				Krige JEJ, Kotze UK, Distiller G, Shaw J and Bornman PC (2009) Predictive factors for rebleeding and death in alcoholic cirrhotic patients with acute variceal bleeding: a multivariate analysis. World Journal of Surgery 33:2127–2135	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				The study by Krige et al (2009) was a fair quality study in 310 patients with acute esophageal variceal bleeding from alcohol related cirrhosis. The study used multivariate analysis to assess the association between a range of risk factors (including INR) and variceal rebleeding and death. Although the study was published relatively recently, it should be noted that the analysis included data collected from patients over a 26 year period. Results from older patients may have limited applicability to the current Australian healthcare setting.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Retrospective cohort study	
Citation:				Kim, H., J. H. Lee, S. J. Choi, J. H. Lee, M. Seol, Y. S. Lee, W. K. Kim, J. S. Lee, and K. H. Lee, 2006, Risk score model for fatal intracranial hemorrhage in acute leukemia: Leukemia, v. 20, no. 5, p. 770–776.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Retrospective cohort study including 792 patients, out of which 67 patients (8.5%) were lost to follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Retrospective cohort study	
Citation:				Dally N, Hoffman R, Haddad N, Sarig G, Rowe JM, Brenner B. Predictive factors of bleeding and thrombosis during induction therapy in acute promyelocytic leukemia-a single center experience in 34 patients. Thromb Res. 2005;116(2):109–14	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
		✓		Was follow-up long enough for outcomes to occur?	III
Comments:				This small prospective cohort study is unlikely to be adequately powered to properly ascertain the influence of various prognostic markers on bleeding. It should be further noted that the study only adjusted for a small number of clinical parameters.	
Quality rating: [Good/Fair/Poor]				Fair	

Different fibrinogen levels

Level II evidence

Study type:				Prospective cohort study	
Citation:				Violi, 1995	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
	✓			Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective population based cohort with relatively long follow-up period.	
Quality rating: [Good/Fair/Poor]				Poor	

Level III evidence

Study type:				Retrospective cohort study	
Citation:				Kim, H., J. H. Lee, S. J. Choi, J. H. Lee, M. Seol, Y. S. Lee, W. K. Kim, J. S. Lee, and K. H. Lee, 2006, Risk score model for fatal intracranial hemorrhage in acute leukemia: Leukemia, v. 20, no. 5, p. 770–776.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
			✓	Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Retrospective cohort study including 792 patients, out of which 67 patients (8.5%) were lost to follow-up.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Retrospective cohort study	
Citation:				Dally N, Hoffman R, Haddad N, Sarig G, Rowe JM, Brenner B. Predictive factors of bleeding and thrombosis during induction therapy in acute promyelocytic leukemia-a single center experience in 34 patients. Thromb Res. 2005;116(2):109–14	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
✓				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
		✓		Was follow-up long enough for outcomes to occur?	III
Comments:				This small prospective cohort study is unlikely to be adequately powered to properly ascertain the influence of various prognostic markers on bleeding. It should be further noted that the study only adjusted for a small number of clinical parameters.	
Quality rating: [Good/Fair/Poor]				Fair	

E6 Quality analysis – Question 6

Level II evidence

Study type:				Cohort study	
Citation:				Masera G, Terzoli S, Avanzini A (1982) Evaluation of the supertransfusion regimen in homozygous beta-thalassaemia children. Br J Haematol 52(1):111–3.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
	✓			Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
		✓		Was loss to follow-up and exclusions from analysis reported?	II
		✓		Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
		✓		Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study of 11 β-thalassaemia patients treated with two consecutive transfusion regimens. No reporting of inclusion/exclusion criteria.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Torcharus K, Withayathawornwong W, Sriphaisal T, Krutvacho T, Arnutti P, Suwanasophorn C (1993) High transfusion in children with beta-thalassemia/Hb E: clinical and laboratory assessment of 18 cases. Southeast Asian J Trop Med Public Health 24 Suppl 1:96–9.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
	✓			Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
			✓	Was loss to follow-up and exclusions from analysis reported?	II
			✓	Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
	✓			Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
Comments:				Prospective cohort study of 18 β-thalassaemia and Hb E patients. Follow-up duration 15 months Patients treated with hyper-transfusion only and standard transfusion only had different baseline pre-transfusion Hb and serum ferritin.	
Quality rating: [Good/Fair/Poor]				Poor	

Level III evidence

			Study type:	Cohort study	
			Citation:	Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P (1997) A moderate transfusion regimen may reduce iron loading in (beta)-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion 37(2):135–40.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
✓				Was loss to follow-up and exclusions from analysis reported?	II
	✓			Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
		✓		Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Retrospective cohort analysis of 32 patients treated with two consecutive transfusion regimens. Three subjects were excluded from the study due to death during the second treatment period.	
			Quality rating: [Good/Fair/Poor]	Fair	

			Study type:	Cohort study	
			Citation:	Roudbari M, Soltani-Rad M, Roudbari S. (2008) The survival analysis of beta thalassemia major patients in South East of Iran. Saudi Med J. 29(7):1031–5.	
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
			✓	Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
			✓	Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
✓				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
	✓			Was loss to follow-up and exclusions from analysis reported?	II
✓				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
✓				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
✓				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
	✓			Was outcome assessment blinded to exposure status?	III
✓				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
✓				Was follow-up long enough for outcomes to occur?	III
			Comments:	Retrospective cohort study of 578 β-thalassaemia patients. Patients lost to follow-up were excluded from analysis. Number of patients excluded not reported. Regression analysis included HB, number of transfusions and co-existing diseases.	
			Quality rating: [Good/Fair/Poor]	Fair	

Appendix F Evidence summaries

F1 Evidence summaries – Question 1

ACS

Level II evidence

STUDY DETAILS: Cohort study		
Citation		
Anker et al (2009) Prevalence, incidence and prognostic value of anaemia in patients after an acute myocardial infarction: data from the OPTIMAAL trial. European Heart Journal 30: 1331–1339.		
Affiliation/Source of funds		
Department of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany; Department of Clinical Cardiology, NHLI London, UK; Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; Department of Academic cardiology, Castle Hill Hospital, Hull, UK; Merck Research laboratories, West Point, PA, US; Department of Cardiology, Rishospitalet, Oslo, Norway; Cardiac Department, Military Hospital, Wroclaw, Poland; Stavanger University Hospital, University of Bergen, Bergen, Norway.		
Study design	Level of evidence	Location/setting
Re-analysis of a double-blind RCT comparing losartan and captopril	Level II	Denmark, Finland, Germany, Ireland, Norway, Sweden, UK
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (categorical and continuous)	Age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Kilip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.	
Population characteristics (including size)		
Diagnosis of acute myocardial infarction and signs or symptoms of heart failure during the acute phase suggested by one or more of the following: treatment with diuretic or intravenous vasodilator therapy for heart failure; pulmonary rales; third heart sound; persistent sinus tachycardia (≥ 100 bpm); radiographic evidence of pulmonary congestion. Also, AMI and a LVEF < 35% or a left-ventricular end-diastolic dimension or greater than 65 mm (optional) and/or a new Q-wave anterior wall AMI, or any reinfarction with previous pathological Q-waves in the anterior wall. Mean age 67.4; female 28.4%; BMI 26.6.		
Length of follow-up	Outcomes measured	
Median 3 years	*All-cause death*; cardiovascular hospitalisation; CHF hospitalisation; any hospitalisation; all-cause death or CHF hospitalisation; *sudden cardiac death; death due to progressive heart failure*	
Method of analysis		

Cox-proportional hazards analysis was performed to assess the association between baseline variables and endpoints. Factors which are known to be of prognostic value in heart failure were included in a multivariable model (see above).				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Re-analysis of a double-blind RCT (OPTIMAAL); 91.5% of 5477 randomised patients who had baseline Hb measurement were included in the analysis (no discussion of characteristics of missing patients); results adjusted for a large number of potential confounders.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	5477			
Analysed	5010			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All-cause mortality N=5010	Anaemia (WHO)	No anaemia	HR 1.35 (1.16, 1.56)	*Anaemia is a significant independent risk factor for all-cause mortality* P<0.0001
Sudden cardiac death N=5010	Anaemia (WHO)	No anaemia	HR 1.14 (0.89, 1.48)	*Anaemia is not an independent risk factor for sudden cardiac death* P=0.303
Death due to progressive heart failure N=5010	Anaemia (WHO)	No anaemia	HR 1.55 (1.13, 2.13)	*Anaemia is a significant independent risk factor for death due to progressive heart failure* P=0.006

Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
All-cause death N=5010	Increase in Hb of 1 SD	HR 0.88 (0.83, 0.93)	*A one SD increase in Hb results in a significantly decreased risk of all-cause mortality* P<0.001
Sudden cardiac death N=5010	Increase in Hb of 1 SD	HR 0.86 (0.80, 1.03)	*A one SD increase in Hb does not result in a significantly decreased risk of sudden cardiac death* P=0.141

Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Death due to progressive heart failure N=5010	Increase in Hb of 1 SD	HR 0.80 (0.69, 0.94)	*A one SD increase in Hb results in a significantly decreased risk of death due to progressive heart failure* P=0.006
All-cause mortality in patients alive at 12 months N=3921	12-month change in Hb of 1 SD	HR 0.73 (0.63, 0.85)	*A 12-month change of Hb of 1 SD results in a significantly decreased risk of all-cause mortality* *P<0.001*
All-cause mortality in patients alive at 12 months N=3921	12-month increase in Hb of 1 SD	HR 0.67 (0.51, 0.81)	*A 12-month increase of Hb of 1 SD results in a significantly decreased risk of all-cause mortality* *P<0.01*
All-cause mortality in patients alive at 12 months N=3921	12-month decrease in Hb of 1 SD	HR 1.27 (1.00, 1.60)	*A 12-month decrease of Hb of 1 SD results in a significantly increased risk of all-cause mortality* *P=0.05*
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of patients with an acute myocardial infarction complicated by heart failure.			
Applicability			
This study was conducted in a large number of subjects in a number of countries and is likely to be applicable to the Australian setting.			
Comments			
The authors conclude that "in patients with complicated AMIs, anaemia on admission and/or reductions in haemoglobin during follow up are independent risk factors for mortality and hospitalisation".			

AMI, acute myocardial infarction; BMI, body mass index; bpm; beats per minute; CHF, congestive heart failure; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; RCT, randomised controlled trial; SD, standard deviation; UK, United Kingdom; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Archbold et al (2006) Hemoglobin concentration is an independent determinant of heart failure in acute coronary syndromes: cohort analysis of 2310 patients. Am Heart J 152: 1091–1095.		
Affiliation/Source of funds		
Newham University Hospital, London, UK; London Chest Hospital London, UK; King George Hospital, Ilford, UK; University College, London, UK. Funding not stated.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	Coronary Care Unit/UK
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (states WHO definition but Hb < 12.5 g/dL used for analyses)	Age, sex, race, diabetes, hypertension, smoking, previous angina, previous ACS, renal function, background aspirin, ACEI, diuretic, statin therapy, heart rate, SBP, reperfusion therapy and ACS presentation.	
Population characteristics (including size)		
Diagnosis of ACS (MI, STEMI, NSTEMI, unstable angina); ~47% had unstable angina; age ~64 years, male ~75%. N=2310		
Length of follow-up	Outcomes measured	
Hospitalisation period	Cardiac death, left ventricular function	
Method of analysis		
Variables with univariate significance were entered into logistic regression analysis to determine independent effects of Hb.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Prospective cohort study based in a cardiac care unit; 2310/3119 (74.1%) had baseline Hb measurements recorded; baseline variables between groups with or without baseline Hb similar with the exception of the proportion of South Asians (34% vs 39%); analysis adjusted for a large number of potential confounders; it is not clear how determination of cardiac death was made and potential for bias due to known Hb status is not addressed; follow-up during hospitalisation.		
RESULTS		
Population	With risk factor	Without risk factor
Available	3119	
Analysed	558	1752

Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
In-hospital cardiac death (N=1140)	Hb < 12.5 g/dL	Hb 12.5–13.6 g/dL	OR 1.56 (0.76, 3.22)[a]	*Hb < 12.5 g/dL is not an independent risk factor for in-hospital cardiac death compared with Hb 12.5–13.6 g/dL* P=NR
In-hospital cardiac death (N=1152)	Hb < 12.5 g/dL	Hb 13.7–14.7 g/dL	OR 1.00 (0.42, 2.36)[a]	*Hb < 12.5 g/dL is not an independent risk factor for in-hospital cardiac death compared with Hb 13.7–14.7 g/dL* P=NR
In-hospital cardiac death (N=1134)	Hb < 12.5 g/dL	Hb > 14.7 g/dL	OR 1.73 (0.76, 3.97)[a]	*Hb < 12.5 g/dL is not an independent risk factor for in-hospital cardiac death compared with Hb >14.7 g/dL* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a broad population with ACS. It should be noted that nearly half of the subjects in this study had a diagnosis of unstable angina.				
Applicability				
This study was conducted in the UK. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The results of this study suggest that anaemia is not an independent risk factor for in-hospital cardiac death in patients with ACS (most commonly unstable angina). This authors note that this result differs from a number of other studies which show anaemia is an independent risk factor. One potential reason for this is the large proportion of included subjects with biomarker negative unstable angina, which resulted in low in-hospital mortality (3%). Thus, this study is possibly underpowered to assess Hb as an independent predictor.				

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; MI, myocardial infarction; NR, not reported; NSTEMI, non-ST-segment elevation myocardial infarction; OR, odds ratio; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; UK, United Kingdom; WHO, World Health Organisation.

[a] Represents the comparison between Hb 12.5–13.6 g/dL versus Hb < 12.6 g/dL.

STUDY DETAILS: Cohort study		
Citation		
Aronson et al (2007) Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction. European Heart Journal 28: 1289–1296.		
Affiliation/Source of funds		
Rappaport Family Faculty of Medicine, Technion, Haifa, Israel. Funding not stated.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	Israel/hospital
Risk factor/s assessed	Potential confounding variables measured	
Haemoglobin (baseline, change during hospitalisation, nadir, discharge)	Age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	
Population characteristics (including size)		
Adults presenting to the intensive coronary care unit with a diagnosis of myocardial infarction who were alive at the time of discharge; mean age ~62, female ~ 25%. N=1390		
Length of follow-up	Outcomes measured	
Median 24 months	Mortality	
Method of analysis		
Cox proportional hazards modelling was performed to test the association between Hb levels are different timepoints and mortality.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Prospective, hospital-based cohort study; 1606 patients willing to participate were identified; 216 excluded due to meeting exclusion criteria (n=194) or missing repeated Hb measurement (n=22); analysis adjusted for a number of potential confounding variables thought to have clinical importance or with P<0.1 in the univariate analysis; mortality ascertained by attempting to contact the patient, reviewing hospital course if rehospitalised, and reviewing national death registry; follow-up median 2 years.		
RESULTS		
Population	With risk factor	Without risk factor
Available	248 (WHO anaemia)	1142
Analysed	248 (WHO anaemia)	1142

Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (N=689)	Baseline Hb ≤ 13.1 g/dL	Baseline Hb ≥ 15.5 g/dL	HR 1.6 (0.9, 2.6)	*Baseline Hb ≤ 13.1 g/dL is not an independent risk factor for* post-discharge mortality *compared with Hb ≥ 15.5 g/dL* P=0.07
Mortality (N=673)	Baseline Hb 13.2–14.3 g/dL	Baseline Hb ≥ 15.5 g/dL	HR 1.2 (0.8, 2.1)	*Baseline Hb 13.2–14.3 g/dL is not an independent risk factor for* post-discharge mortality *compared with Hb ≥ 15.5 g/dL* P=0.07
Mortality (N=684)	Baseline Hb 14.4–15.4 g/dL	Baseline Hb ≥ 15.5 g/dL	HR 1.2 (0.7, 2.1)	*Baseline Hb 14.4–15.4 g/dL is not an independent risk factor for* post-discharge mortality *compared with Hb ≥ 15.5 g/dL* P=0.07
Mortality (N=678)	Decrease in Hb during hospitalisation ≥ 2.3 g/dL	Decrease in Hb during hospitalisation ≤ 0.5 g/dL	HR 1.7 (1.1, 2.8)	*A decrease in Hb during hospitalisation of ≥ 2.3 g/dL is an independent risk factor for increased post-discharge mortality compared with a decrease of ≤ 0.5 g/dL* P=0.03
Mortality (N=687)	Decrease in Hb during hospitalisation 1.4–2.2 g/dL	Decrease in Hb during hospitalisation ≤ 0.5 g/dL	HR 1.3 (0.8, 2.2)	*A decrease in Hb during hospitalisation of 1.4–2.2 g/dL is not an independent risk factor for post-discharge mortality compared with a decrease of ≤ 0.5 g/dL* P=0.25
Mortality (N=699)	Decrease in Hb during hospitalisation 0.6–1.3 g/dL	Decrease in Hb during hospitalisation ≤ 0.5 g/dL	HR 1.3 (0.7, 2.1)	*A decrease in Hb during hospitalisation of 0.6–1.3 g/dL is not an independent risk factor for post-discharge mortality compared with a decrease of ≤ 0.5 g/dL* P=0.25

Mortality (N=691)	Nadir Hb ≤ 11.3 g/dL	Nadir Hb ≥ 14.0 g/dL	HR 3.3 (1.7, 6.3)	Nadir Hb ≤ 11.3 g/dL is an independent risk factor for increased post-discharge mortality compared with nadir Hb ≥ 14.0 g/dL P<0.001
Mortality (N=698)	Nadir Hb 11.4–12.8 g/dL	Nadir Hb ≥ 14.0 g/dL	HR 2.1 (1.1, 4.1)	Nadir Hb 11.4–12.8 g/dL is an independent risk factor for increased post-discharge mortality compared with nadir Hb ≥ 14.0 g/dL P=0.03
Mortality (N=683)	Nadir Hb 12.9–13.9 g/dL	Nadir Hb ≥ 14.0 g/dL	HR 1.1 (0.5, 2.3)	Nadir Hb 12.9–13.9 g/dL is not an independent risk factor for increased post-discharge mortality compared with nadir Hb ≥ 14.0 g/dL P=0.83
Mortality (N=685)	Discharge Hb ≤ 11.9 g/dL	Discharge Hb ≥ 14.6 g/dL	HR 2.6 (1.5, 4.7)	Discharge Hb ≤ 11.9 g/dL is an independent risk factor for increased post-discharge mortality compared with discharge Hb ≥ 14.6 g/dL P=0.001
Mortality (N=691)	Discharge Hb 12.0–13.3 g/dL	Discharge Hb ≥ 14.6 g/dL	HR 2.0 (1.1, 3.7)	Discharge Hb 12.0–13.3 g/dL is an independent risk factor for increased post-discharge mortality compared with discharge Hb ≥ 14.6 g/dL P=0.03
Mortality (N=696)	Discharge Hb 13.3–14.5 g/dL	Discharge Hb ≥ 14.6 g/dL	HR 1.4 (0.7, 2.7)	Discharge Hb 13.3–14.5 g/dL is not an independent risk factor for increased post-discharge mortality compared with discharge Hb ≥ 14.6 g/dL P=0.32

Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Mortality (N=1390)	Baseline Hb (1 g/dL decrease)	HR 1.10 (0.99, 1.21)	A 1 g/dL decrease in Hb at baseline is not an independent risk factor for increased post-discharge mortality P=0.06
Mortality (N=1390)	Decrease in Hb during hospitalisation (1 SD)	HR 1.21 (1.0, 1.45)	A 1 SD decrease in Hb during hospitalisation is an independent risk factor for increased post-discharge mortality P=0.03
Mortality (N=1390)	Nadir Hb (1 g/dL decrease)	HR 1.36 (1.19, 1.55)	A 1 g/dL decrease in nadir Hb is an independent risk factor for increased post-discharge mortality P<0.001
Mortality (N=1390)	Discharge Hb (1 g/dL decrease)	HR 1.27 (1.16, 1.40)	A 1 g/dL decrease in discharge Hb is an independent risk factor for increased post-discharge mortality P<0.001
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to adults hospitalised for myocardial infarction without known malignancy, inflammatory disease, surgery or trauma within the previous month, who survived hospitalisation.			
Applicability			
This study was conducted in Israel. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors conclude that "anaemia during the course of hospital stay and at discharge is a predictor of long-term mortality and HF in survivors of AMI and provides prognostic information beyond that provided by recognized risk factors and the degree of LV systolic dysfunction". The authors note a number of limitations of their study including: (i) the fact that the study excluded subjects who died during hospitalisation probably decreased the power of the analysis to detect an association between baseline Hb and mortality; (ii) as Hb was not always measured daily throughout hospitalisation after the 3rd day, nadir Hb may have potentially been misclassified; and (iii) Hb was not measured post-discharge so the prognostic implications of persistent vs transient Hb could not be determined.			

AMI, acute myocardial infarction; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HF, heart failure; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; SD, standard deviation; WHO, World Health Organisation.

STUDY DETAILS: Cohort study			
Citation			
Bassand et al (2010) Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes. European Heart Journal 31: 50–58.			
Affiliation/Source of funds			
University Hospital Jean Minjoz, France; McMaster University, Hamilton, Canada; University Hospital Uppsala, Uppsala, Sweden; Academic Medical Center, Amsterdam, the Netherlands; Growchowski Hospital, Warsaw, Poland; University of Edinburgh, Edinburgh, UK; University of Toronto, Toronto, Canada; Duke Clinical Research Institute, Durham, US. Oasis 5 and 6 trials were funded by Sanofi Aventis, Organon, and GlaxoSmithKline. This study conducted independently by the Steering Committee and the Population health Research Institute, McMaster University and Hamilton health Sciences, Hamilton, Ontario, Canada.			
Study design	Level of evidence	Location/setting	
Cohort analysis of 2 RCTs	Level II	Various/hospital	
Risk factor/s assessed	Potential confounding variables measured		
Hb (continuous)	Baseline demographics, prior medical history, cardiovascular risk factors, randomised treatment allocation, co-interventions.		
Population characteristics (including size)			
Patients presenting to hospital with symptoms of NSTE-ACS or STEMI; age 64.7 years; male 65.7%. N= 31,939			
Length of follow-up	Outcomes measured		
30 days	Bleeding; death; death/MI		
Method of analysis			
Logistic regression models were used to determine independent predictors of outcomes.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Cohort analysis of pooled data from two RCTs; no details provided on number of eligible subjects included in analysis but data came from two RCTs so may have been good follow-up and little missing data; analyses adjusted for a variety of potential confounders; all outcome assessment conducted blind to treatment assignment; 30 day follow-up.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	32,170		
Analysed	6565	25,374	
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
30-day mortality (N=28,907) Patients with baseline Hb < 15.9	Hb increase (1 g/dL)	OR 0.94 (0.90, 0.98)	*A 1 g/dL increase in Hb results in a 6% decreased risk of mortality* P=NR

30-day mortality/MI (N=28,907) Patients with baseline Hb < 15.9	Hb increase (1 g/dL)	OR 0.96 (0.93, 0.99)	*A 1 g/dL increase in Hb results in a 4% decreased risk of mortality/MI* P=NR
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population with ACS with or without ST-segment elevation.			
Applicability			
The data included in this study was collected in a large number of countries (including Australia). The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors conclude that low Hb is an independent risk factor for bleeding, death and death or MI at 30 days. Other independent risk factors for death and death or MI at 30 days included treatment allocation, age, heart failure, PCI, diabetes and creatinine clearance. The authors note a number of limitations of their study including the possibility of residual confounding and the lack of known cause of the anaemia.			

ACS, acute coronary syndrome; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; RCT, randomised controlled trial; STEMI, ST-segment elevation myocardial infarction; UK, United Kingdom; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Burr et al (1992) Haematological prognostic indices after myocardial infarction: evidence from the diet and reinfarction trial (DART). European Heart Journal 13: 166–170.		
Affiliation/Source of funds		
MRC Epidemiology Unit, Penarth, UK; Frenchay Hospital, Bristol, UK. Supported by grants from the Welsh Scheme for the development of Health and Social Research and the Health Promotion Trust.		
Study design	Level of evidence	Location/setting
Cohort analysis of a RCT (DART)	Level II	Community/UK
Risk factor/s assessed	Potential confounding variables measured	
Haematological indices (including Hb)	Age, smoking, energy, diet group.	
Population characteristics (including size)		
Non-diabetic men aged < 70 years recovering from MI; age ~ 56. N=1755		
Length of follow-up	Outcomes measured	
18 months	Mortality	
Method of analysis		
A Cox proportional hazards regression analysis was carried out in order to examine the relationship between the haematological variables and mortality.		

INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: Cohort analysis of a dietary RCT (DART); of 2033 who entered trial, 1877 were seen at the 6 month visit where blood was taken (most of the others died); blood taken from 1755 subjects; no details given on subjects missing from the analysis; analysis adjusted but for very few variables and not those commonly adjusted for in other analyses; 18 months follow-up.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	1755		
Analysed	1755		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Mortality (N=1755)	Hb change (1 SD)	SOR 0.72	*A 1 SD change in Hb is an independent risk factor for decreased mortality* P<0.001
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of non-diabetic men recovering from MI.			
Applicability			
This study was conducted in the UK. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors conclude that "haematological variables have an important prognostic significance after myocardial infarction". With regards to Hb, the authors note surprise with the negative association between mortality and Hb, stating that a previous study in women showed increased cardiovascular mortality in women with higher haematocrit values.			

CI, confidence interval; Hb, haemoglobin; MI, myocardial infarction; MRC, medical research council; RCT, randomised controlled trial; SD, standard deviation; SOR, standardised odds ratio; UK, United Kingdom.

STUDY DETAILS: Cohort study		
Citation		
Cavusoglu et al (2006) Usefulness of anaemia in men as an independent predictor of two-year cardiovascular outcome in patients presenting with acute coronary syndrome. Am J Cardiol 98: 580–584.		
Affiliation/Source of funds		
SUNY Downstate Medical Center, Brooklyn, US; Bronx Veterans Affairs Medical Center, Bronx, US. Funding not reported		
Study design	Level of evidence	Location/setting
Prospective, hospital-based cohort	Level II	Hospital/US

Risk factor/s assessed	Potential confounding variables measured
Anaemia (WHO) and Hb level	Age, number of diseased coronary arteries, left ventricular function, haemoglobin, serum creatinine.

Population characteristics (including size)				
Men with ACS (ST-elevation AMI, non-ST segment elevation AMI and unstable angina pectoris); mean age ~ 65 years. N=191				
Length of follow-up	Outcomes measured			
2 years	Death/MI			
Method of analysis				
Multivariate Cox proportional hazards analysis was performed as stepwise regressions with backward elimination to identify independent predictors.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective, hospital-based cohort study; 193 men eligible, 191 with Hb values, 100% follow-up; analysis adjusted for potential confounders identified by univariate analysis, however race was not included; mortality data obtained by review of Social Security Death Index, medical records, next of kin or primary physician; MI diagnosed using specific troponin values; follow-up 2 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	193			
Analysed	80		111	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Death/MI (N=191)	Anaemia (WHO)	No anaemia	HR 1.86 (1.02, 3.40)	*Anaemia is an independent risk factor for death/MI* P=0.0429
Death/MI (N=NR)	Hb < 10.5	Hb > 12.5	HR 2.37 (0.94, 5.99)	*Anaemia may be an independent risk factor for death/MI* P=0.0681
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value
Death/MI (N=191)	Hb increase (1 g/dL)		HR 0.74 (0.55, 0.99)	*A 1 g/dL increase in Hb is associated with a decreased risk of death/MI* P=0.0411
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a male population with ACS.				
Applicability				
This study was conducted at a single centre in the US. The results of this study are likely to be applicable to the Australian population.				

Comments
The authors conclude that there is a "strong and statistically significant independent association between low haemoglobin concentrations and the adverse cardiovascular outcomes of death and AMI at 24 months). The authors note a number of limitations of their study, in particular the inability to explore in detail the 3 subgroups of ACS patients due to the small sample size, which may also have affected their analysis of the lower vs higher Hb groups. One potential issue identified during the evaluation of this study is the lack of adjustment for race in the analyses, given that the largest proportion of the population were Black or Hispanic. A number of other studies have suggested differences in the association between anaemia and mortality by race.

AMI, acute myocardial infarction; ACS, acute coronary syndrome; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; MI, myocardial infarction; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Giraldez et al (2009) Baseline haemoglobin concentration and creatinine clearance composite laboratory index improves risk stratification in ST-elevation myocardial infarction. Am Heart J 157: 517–524.		
Affiliation/Source of funds		
Harvard Medical School, Boston, US. Funding not stated.		
Study design	Level of evidence	Location/setting
Prospective hospital-based cohort analysis of 2 RCTs	Level II	US/hospital-based
Risk factor/s assessed	Potential confounding variables measured	
Hb and creatinine clearance	Age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	
Population characteristics (including size)		
Experimental set (In-TIME II-TIMI 17): patients presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI; age 61.2 years, male 75.3%. N=14,799 Validation set (ExTRACT-TIMI 25): Patients with STEMI: Baseline characteristics not stated. N=18,427		
Length of follow-up	Outcomes measured	
30 days	30-day mortality	
Method of analysis		
A multivariable logistic regression model was used to evaluate the independent relationship between each laboratory test (ie, Hb or CrCl) and all-cause mortality through 30 days and included potential confounding factors.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Cohort analysis of a 2 prospective RCTs, one used to define a laboratory index and the other to validate it; 14,373/14,799 (97%) included in analysis from the first trial and 18,400/18,427 (99.9%) from the second trial; therefore, some subjects with missing data excluded from the analysis but this was a very small percentage; analysis adjusted for a large number of potential confounding factors; 30 day follow-up.		

RESULTS				
Population	With risk factor		Without risk factor	
Available	See above			
Analysed	See above			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
30-day mortality (N=3667) InTIME II-TIMI 17	Hb < 11 g/dL	Hb 15–16 g/dL	OR 2.51 (1.68, 3.74)	*A Hb level < 11 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P<0.001
30-day mortality (N=3899) InTIME II-TIMI 17	Hb 11–12 g/dL	15–16 g/dL	OR 2.25 (1.62, 3.15)	*A Hb level 11–12 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P<0.001
30-day mortality (N=4739) InTIME II-TIMI 17	Hb 12–13 g/dL	15–16 g/dL	OR 1.83 (1.40, 2.39)	*A Hb level 12–13 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P<0.001
30-day mortality (N=6351) InTIME II-TIMI 17	Hb 13–14 g/dL	15–16 g/dL	OR 1.39 (1.09, 1.76)	*A Hb level 13–14 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P=0.008
30-day mortality (N=7549) InTIME II-TIMI 17	Hb 14–15 g/dL	15–16 g/dL	OR 1.11 (0.88, 1.40)	*A Hb level 14–15 g/dL is not an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P=0.40
30-day mortality (N=4449) ExTRACT-TIMI 25	Hb < 11 g/dL	15–16 g/dL	OR 1.82 (1.30, 2.57)	*A Hb level < 11 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P<0.01
30-day mortality (N=4848) ExTRACT-TIMI 25	Hb 11–12 g/dL	15–16 g/dL	OR 1.39 (1.03, 1.88)	*A Hb level 11–12 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P=0.03

30-day mortality (N=5966) ExTRACT-TIMI 25	Hb 12–13 g/dL	15–16 g/dL	OR 1.33 (1.04, 1.70)	*A Hb level 12–13 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P=0.02
30-day mortality (N=7676) ExTRACT-TIMI 25	Hb 13–14 g/dL	15–16 g/dL	OR 1.22 (0.98, 1.53)	*A Hb level 13–14 g/dL is not an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P=0.08
30-day mortality (N=8911) ExTRACT-TIMI 25	Hb 14–15 g/dL	15–16 g/dL	OR 1.05 (0.84, 1.31)	*A Hb level 14–15 g/dL is not an independent risk factor for 30-day mortality compared with a Hb level 15–16 g/dL* P=0.69
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value
30-day mortality (N=14,373) InTIME-TIMI 17	Hb 1 g/dL decrease		OR 1.22 (1.15, 1.29)	*A 1 g/dL decrease in Hb in patients with baseline Hb < 15 g/dL significantly increases the risk of 30-day mortality* P<0.001
30-day mortality (N=18,400) ExTRACT-TIMI 25	Hb 1 g/dL decrease		OR 1.10 (1.04, 1.16)	*A 1 g/dL decrease in Hb in patients with baseline Hb < 15 g/dL significantly increases the risk of 30-day mortality* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with STEMI. However, the authors note that patients with higher risk profiles and those who were fibrinolytic ineligible were excluded so that limits generalisable to the entire STEMI population.				
Applicability				
This study was conducted at a single centre in the US. The results of this study are likely to be applicable to the Australian population.				
Comments				
The authors conclude that the combination of laboratory predictors of mortality (ie, Hb and CrCl) into a single laboratory index can be used for risk assessment. The authors note a number of limitations of their study including the narrow population included, and possible residual confounding.				

CI, confidence interval; dL, decilitre; ECG, electrocardiograph; g, grams; Hb, haemoglobin; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; US, United States of America.

STUDY DETAILS: Cohort study				
Citation				
Hasin et al (2009) Prevalence and prognostic significance of transient, persistent and new-onset anemia after acute myocardial infarction. Am J Cardiol 104: 486–491.				
Affiliation/Source of funds				
Ramban Medical Center and the Bruce Rappaport Faculty of Medicine and Research Institute, Haifa, Israel.				
Study design	Level of evidence		Location/setting	
Prospective hospital-based cohort study	Level II		Hospital/Israel	
Risk factor/s assessed		Potential confounding variables measured		
Anaemia (WHO) and Hb		Age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Kilip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.		
Population characteristics (including size)				
Patients with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥ 28 days after hospital discharge; age ~ 61 years, female ~20%. N=1065				
Length of follow-up		Outcomes measured		
Mean 27 months following post-discharge Hb measurement		Mortality or heart failure		
Method of analysis				
Cox proportional hazards regression with backward selection used to calculate adjusted hazard ratios.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Analysis based on data from a prospective hospital-based cohort database; of 1805 discharged from hospital with AMI, 1065 with post-discharge Hb measurement who remained alive after 28 days were included in the analysis; all 1065 included in analysis so assume no loss to follow-up; adjusted for a large number of potential confounders; mortality and heart failure measured via national death registry, patient contact and reviewing hospital course; follow-up mean 27 months (12–44) following post-discharge Hb measurement.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	370		695	
Analysed	370		695	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value

Mortality or heart failure (N=802) All patients	Anaemia (WHO) resolved	No anaemia	HR 0.8 (0.5, 1.3)	*Resolved anaemia is not an independent risk factor for mortality or heart failure* P=0.40
Mortality or heart failure (N=695) All patients	New-onset anaemia (WHO)	No anaemia	HR 1.9 (1.1, 3.3)	*New-onset anaemia is an independent risk factor for mortality or heart failure* P=0.03
Mortality or heart failure (N=848) All patients	Persistent anaemia (WHO)	No anaemia	HR 1.8 (1.2, 2.5)	*Persistent anaemia is an independent risk factor for mortality or heart failure* P=0.003
Mortality or heart failure (N=753) No malignancy	Anaemia (WHO) resolved	No anaemia	HR 0.8 (0.5, 1.4)	*Resolved anaemia is not an independent risk factor for mortality or heart failure* *P=0.47*
Mortality or heart failure (N=653) No malignancy	New-onset anaemia (WHO)	No anaemia	HR 1.9 (1.1, 3.6)	*New-onset anaemia is an independent risk factor for mortality or heart failure* *P<0.001*
Mortality or heart failure (N=781) No malignancy	Persistent anaemia (WHO)	No anaemia	HR 1.7 (1.2, 2.6)	*Persistent anaemia is an independent risk factor for mortality or heart failure* *P=0.008*
Mortality or heart failure (N=743) No anaemia at baseline	Anaemia (WHO) resolved	No anaemia	HR 0.7 (0.4, 1.4)	*Resolved anaemia is not an independent risk factor for mortality or heart failure* *P=0.31*
Mortality or heart failure (N=659) No anaemia at baseline	New-onset anaemia (WHO)	No anaemia	HR 1.7 (1.0, 3.3)	*New-onset anaemia may be an independent risk factor for mortality or heart failure* *P=0.05*
Mortality or heart failure (N=720) No anaemia at baseline	Persistent anaemia (WHO)	No anaemia	HR 1.8 (1.1, 2.8)	*Persistent anaemia is an independent risk factor for mortality or heart failure* *P=0.01*
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value

Mortality or heart failure (N=1065) All patients	1 SD decrease in Hb from discharge to follow-up measurement	HR 1.48 (1.25, 1.75)	*A 1 SD decrease in Hb results in a 48% increased risk of mortality or heart failure* P<0.001
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population who survived at least 28 days post-hospital discharge.			
Applicability			
This study was conducted in Israel. The results of this study are likely to be generalisable to the Australian population.			
Comments			
The authors note that "anemia late after AMI has important prognostic implications" and that there are limitations in measuring anaemia at only a single time point. They have shown that while resolved anaemia is not associated with an increased risk, both new-onset anaemia and persistent anaemia are. They note a number of limitations of their study including (i) only partial follow-up of blood counts; and (ii) no information on the cause of anaemia.			

ACEI, angiotensin-converting enzyme inhibitor; AIIRA, angiotensin II receptor antagonists; AMI, acute myocardial infarction; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; SD, standard deviation; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Keough-Ryan et al (2005) Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions and anaemia. Am J Kidney Dis 46: 845–855.		
Affiliation/Source of funds		
Dalhousie University, Halifax, Canada; McMaster University, Hamilton, Canada. Funding not stated.		
Study design	Level of evidence	Location/setting
Cohort study using a prospective population-wide registry	Level II	Hospital/Canada
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (mild, moderate and severe); chronic renal insufficiency, cardiac interventions.	Age, sex, diabetes, hypertension, smoking, previous CABG, cardiac catheterization, CABG, thrombolysis, medications on discharge. Note: a large number of potential confounders not considered (including BMI, history of MI, peripheral vascular disease, cerebrovascular accident, TIA, CHF, family history of ischaemic heart disease) due to missing data.	
Population characteristics (including size)		
Adults admitted to hospital with a discharge diagnosis of acute coronary syndrome who survived to discharge; mean age 66.1 years, male 61.2%. N=5549.		
Length of follow-up	Outcomes measured	

Mean 5.6 years	Death, length of stay, surgical intervention, medication use at discharge.

Method of analysis

Cox proportional-hazards modelling was used to examine the relationship of survival with risk factors including anaemia. Forward stepwise models were used.

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Poor

Description: Cohort analysis of a prospective population-based registry; 6587 had a discharge diagnosis of ACS, 84% (5549) included in analysis – 457 of those excluded died in hospital, 38 had end stage renal disease and 543 had extreme or missing creatinine values; analyses adjusted for a number of confounders but authors note that many other potential confounders not considered due to missing data; outcomes data collected via linkage to Vital Statistics registry; follow-up mean 5.6 years.

RESULTS

Population	With risk factor		Without risk factor	
Available	6130			
Analysed	5549			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (N=NR)	Mild anaemia (Hb 10.5–12.0 g/dL)	No anaemia (Hb > 12.0 g/dL)	HR 0.968 (0.924, 1.015)	*Mild anaemia is not an independent risk factor for mortality* P=NR
Mortality (N=NR)	Moderate anaemia (Hb 9.0–10.5 g/dL)	No anaemia (Hb > 12.0 g/dL)	HR 1.050 (0.965, 1.114)	*Moderate anaemia is not an independent risk factor for mortality* P=NR
Mortality (N=NR)	Severe anaemia (Hb < 9.0 g/dL)	No anaemia (Hb > 12.0 g/dL)	HR 1.376 (1.179, 1.606)	*Severe anaemia is an independent risk factor for mortality* P=NR

EXTERNAL VALIDITY

Generalisability

The results of this study are generalisable to an adult population hospitalised with ACS without end stage renal failure who survived to hospital discharge.

Applicability

This study was conducted in Canada. The results of this study are likely to be applicable to the Australian setting.

Comments

Apart from severe anaemia, a number of other factors were shown to be independently associated with increased mortality; these included moderate and severe chronic renal insufficiency, diabetes, current smoking, increased age class, male sex, diagnosis of CHF on discharge, use of ACEIs, ARBs or diuretics on discharge. The authors note a number of limitations of their study including (i) missing event data in subjects who had left the Province or had events outside the Province; (ii) the limited generalisability to those hospitalised for an event (ie, excludes those with an event who were not hospitalised); and (iii) the fact that prescribing practices would have changed since the cohort dates of 1997–1999.

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; MI, myocardial infarction; NR, not reported; TIA, transient ischemic attack.

STUDY DETAILS: Cohort study		
Citation		
Mahaffey et al (2007) Prediction of one-year survival in high-risk patients with acute coronary syndromes: results from the SYNERGY trial. J Gen Intern Med 23(3): 310–316.		
Affiliation/Source of funds		
Duke Clinical Research Institute, Durham, US; Brigham and Women's Hospital, Boston, US; Auckland City Hospital, Auckland, New Zealand; St Michael's Hospital, Toronto, Canada; Newark Beth Israel Medical Centre, Newark, US; The Methodist DeBakey Heart Center, Houston, US; Flinders Medical Centre, Adelaide, Australia; Clinique Universitaire St. Luc., Brussels, Belgium; Texas Heart Institute, Houston, US. The SYNERGY trial was funded by Sanofi Aventis.		
Study design	Level of evidence	Location/setting
Prospective cohort analysis of a RCT (SYNERGY)	Level II	Hospital/US, Canada, New Zealand, Australia, Belgium

Risk factor/s assessed	Potential confounding variables measured
Various including Hb	Age, sex, weight, height, race, time from symptoms to randomisation, region of the world, smoking status, creatinine clearance, Killip class, systolic and diastolic blood pressures, ST-segment elevation and depression, T-wave inversion, diabetes, hypertension, concomitant medications, prior coronary artery disease, recent angina, prior congestive heart failure, prior PCI, prior CABG, criteria for enrolment, heart rate, rales, haemoglobin, haematocrit and platelet count.

Population characteristics (including size)
Patients with ischaemic symptoms lasting for at least 10 minutes occurring within 24 hours of enrolment and at least 2 of the following features: (i) age ≥ 60 years; (ii) troponin or creatinine kinase-MB elevation above the upper limit of normal for the local laboratory; or (iii) definitive ST-segment changes on 12-lead electrocardiograph; age ~67 years, male ~66%. N=9978

Length of follow-up	Outcomes measured
Up to 1 year	30-day mortality; 1-year mortality

Method of analysis
A series of multivariable Cox proportional-hazards models were constructed to identify independent predictors of mortality.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good Description: Cohort analysis of a RCT; 10,027 enrolled in the study but 9978 available for analysis due to problem with randomisation in 49 patients; complete follow-up available in 99.4% (9922); analysis adjusted for a large number of potential confounders; mortality ascertained via phone, medical records, national death indices or a private locator service (US only); follow-up up to 1 year.
RESULTS

Population	With risk factor	Without risk factor
Available	9978	
Analysed	9978	

Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
30-day mortality (N=9978)	1 g/dL increase of Hb (truncated at 15 g/dL)	NR	*A 1 g/dL increase in Hb (up to 15 g/dL) is not associated with an increased risk in 30-day mortality* P=NR
1-year mortality (N=9978)	1 g/dL increase of Hb (truncated at 15 g/dL)	NR	*A 1 g/dL increase in Hb (up to 15 g/dL) is not associated with an increased risk in 1-year mortality* P=NR
1-year mortality in patients surviving through 30 days (N=9664)	1 g/dL increase of Hb (truncated at 15 g/dL)	HR 0.805 (0.748, 0.868)	*A 1 g/dL increase in Hb (up to 15 g/dL) is significantly associated with an decreased risk in 1-year mortality* P=NR
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of high-risk patients with ACS.			
Applicability			
The study was conducted in a number of countries including Australia, New Zealand, Canada, the US and Belgium. The results of this study are likely to be applicable to the Australian setting.			
Comments			
A large number of factors were found to be independent predictors of 30-day mortality, 1-year mortality and 1-year mortality in subjects with ACS surviving the first 30 days. Hb was only significantly associated with the latter outcome. The authors note a number of limitations of their study including (i) the open-label trials design (although they note that with a follow-up of mortality of > 99% this is unlikely to be an issues; (ii) the possibility of residual confounding; and (iii) the limited generalisability of the study due to the specific high-risk patient group.			

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Valeur et al (2009) Anaemia is an independent predictor of mortality in patients with left ventricular systolic dysfunction following acute myocardial infarction. European Journal of Heart Failure 8: 577–584.		
Affiliation/Source of funds		
Rigshospitalet, Copenhagen, Denmark; University of Glasgow, Glasgow, UK; Bispebjerg Hospital, Copenhagen, Denmark. TRACE was sponsored by a grant from Roussel-Uclaf and Knoll		
Study design	Level of evidence	Location/setting

Cohort analysis of a RCT (TRACE)	Level II		Hospital/Denmark	
Risk factor/s assessed		Potential confounding variables measured		
Anaemia (WHO + other definitions)		Age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.		
Population characteristics (including size)				
Patients with left ventricular systolic dysfunction 2–6 days following enzyme-verified AMI; age ~ 68 years, male ~73%. N=1731.				
Length of follow-up		Outcomes measured		
10–12 years		All-cause Mortality		
Method of analysis				
Cox-proportion hazards models used to identify anaemia as an independent predictor.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Cohort analysis of RCT data; Hb measurement missing in only 18 of 1749 (1%) of subjects; analysis adjusted for a large number of potential confounders; follow-up 10–12 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	1749			
Analysed	437		1294	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (N=1731) All patients	Anaemia (WHO)	No anaemia	HR 1.06 (0.93, 1.21)	*Anaemia is not an independent predictor of mortality* P=0.38
Mortality (N=1558) All patients	Mild anaemia (11.0-<12.0 g/dL in women; 12.0-< 13.0 g/dL in men)	No anaemia	HR 0.96 (0.82, 1.13)	Mild anaemia is not an independent predictor of mortality P=0.65
Mortality (N=1408) All patients	Moderate anaemia (10.0-<11.0 g/dL in women; 11.0-< 12.0 g/dL in men)	No anaemia	HR 1.08 (0.86, 1.36)	Moderate anaemia is not an independent predictor of mortality P=0.50
Mortality (N=1353) All patients	Severe anaemia (<10.0 g/dL in women; <11.0 g/dL in men)	No anaemia	HR 1.59 (1.20, 2.11)	Severe anaemia is an independent predictor of mortality P=0.001
Mortality (N=NR) All patients	Lowest decile anaemia (<11.0 g/dL in women; <12.0 g/dL in men)	No anaemia	HR 1.24 (1.04, 1.48)	Lowest decile anaemia is an independent predictor of mortality P=0.017

Mortality (N=1195) Heart failure patients	Anaemia (WHO)	No anaemia	HR 1.16 (1.01, 1.34)	Anaemia is an independent predictor of mortality P=0.048
Mortality (N=1069) Heart failure patients	Mild anaemia (11.0-<12.0 g/dL in women; 12.0-< 13.0 g/dL in men)	No anaemia	HR 1.05 (0.88, 1.25)	Mild anaemia is not an independent predictor of mortality P=0.60
Mortality (N=960) Heart failure patients	Moderate anaemia (10.0-<11.0 g/dL in women; 11.0-< 12.0 g/dL in men)	No anaemia	HR 1.20 (0.93, 1.56)	Moderate anaemia is not an independent predictor of mortality P=0.17
Mortality (N=928) Heart failure patients	Severe anaemia (<10.0 g/dL in women; <11.0 g/dL in men)	No anaemia	HR 1.65 (1.21, 2.25)	Severe anaemia is an independent predictor of anaemia P=0.002
Mortality (N=NR) Heart failure patients	Lowest decile anaemia (<11.0 g/dL in women; <12.0 g/dL in men)	No anaemia	HR 1.32 (1.08, 1.61)	Lowest decile anaemia is an independent predictor of mortality P=0.007
Mortality (N=536) No heart failure	Anaemia (WHO)	No anaemia	HR 0.76 (0.57, 1.02)	Anaemia is not an independent risk factor for mortality P=0.07
Mortality (N=489) No heart failure	Mild anaemia (11.0-<12.0 g/dL in women; 12.0-< 13.0 g/dL in men)	No anaemia	Incorrect[a]	Mild anaemia is not an independent risk factor for mortality P=0.5
Mortality (N=448) No heart failure	Moderate anaemia (10.0-<11.0 g/dL in women; 11.0-< 12.0 g/dL in men)	No anaemia	HR 0.80 (0.49, 1.29)	Moderate anaemia is not an independent risk factor for mortality P=0.36
Mortality (N=425) No heart failure	Severe anaemia (<10.0 g/dL in women; <11.0 g/dL in men)	No anaemia	HR 1.18 (0.58, 2.41)	Severe anaemia is not an independent risk factor for mortality P=0.64
Mortality (N=NR) No heart failure	Lowest decile anaemia (<11.0 g/dL in women; <12.0 g/dL in men)	No anaemia	HR 0.99 (0.66, 1.49)	Lowest decile anaemia is not an independent risk factor for mortality P=0.96
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with left ventricular systolic dysfunction following myocardial infarction, with or without heart failure.				
Applicability				

This study was conducted in Denmark. The results of this study are likely to be applicable to the Australian setting.
Comments
In this specific population, anaemia as defined by the WHO was not an independent predictor of mortality. More severe anaemia was an independent predictor. The authors note that the prognostic importance of anaemia was confined to the first year following AMI, which they state is an important new finding. The study also found that an interaction with heart failure was found, whereby anaemia was only associated with mortality in patients with heart failure. The authors note a number of limitations including (i) the aetiology of anaemia is not known and that prognosis may vary; and (ii) the data was collected in 1990–1992 and treatment regimens have changed since then.

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; BMI, body mass index; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; RCT, randomised controlled trial; WHO, World Health Organisation.

[a] Shown in Table 4 of publication as 0.70 (0.99, 1.00). P value = 0.5.

Heart failure

Level I/III evidence

STUDY DETAILS: SR/MA				
Citation				
Groenveld HF, Januzzi JL, Damman K et al (2008) Anemia and mortality in heart failure patients. A systematic review and meta-analysis. Journal of the American College of Cardiology 52: 818–827.				
Affiliation/Source of funds				
University Medical Center Groningen, The Netherlands; Massachusetts General Hospital, Harvard Medical School, US; Deventer Hospital, The Netherlands. Dr Dannan is supported by the Netherlands Heart Foundation; Dr van Veldhuisen is a Clinical Established Investigator of the Netherlands Heart Foundation; Dr van der Meer is supported by the Dutch Scientific Organization.				
Study design			Level of evidence	Location/setting
Systematic review of literature. Includes data from 34 studies including 8 prospective cohort studies, 9 secondary analyses of RCTs, and 17 retrospective cohort studies.			Level I (aetiology)	Various
Intervention/risk factor			Comparator	
Anaemia (dependant on each author's individual definition and varied across studies from <11–13.0 g/dL Hb or <35%–<40% Ht)			No anaemia	
Population characteristics				
Age > 18 years; diagnosed with chronic heart failure (diastolic or systolic)-definitions of CHF varied across studies.				
Length of follow-up		Outcomes measured		
Ranged from 6 months to 5 years		All-cause mortality		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Good quality systematic review with comprehensive literature search, assessment of individual study quality and exploration of heterogeneity and subgroup analysis.				
RESULTS				
Outcome No. trials (No. patients)	Anaemia n/N (%)	No anaemia n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
CHF				
All-cause mortality 33 studies (N=152,770)	26687/56943 (46.9)	28274/95827 (29.5)	uOR 1.96 (1.74, 2.21)	Anaemia significantly increases all-cause mortality P<0.001 *Heterogeneity I^2=92.4%*

Diastolic CHF				
All-cause mortality 5 studies (N=20,924)	NR	NR	uOR 2.09 (1.53, 2.86)	Anaemia significantly increases all-cause mortality P<0.001 *Heterogeneity NR*
Systolic CHF				
All-cause mortality 12 studies (N=40,025)	NR	NR	uOR 1.96 (1.70, 2.25)	Anaemia significantly increases all-cause mortality P<0.001 *Heterogeneity NR*
CHF (excluding two largest studies)				
All-cause mortality 31 studies (N=42,593)	4587/10201 (45.0)	8191/32392 (25.3)	uOR 1.95 (1.78, 2.14)	Anaemia significantly increases all-cause mortality P<0.001 *Heterogeneity I^2=NR*
CHF (WHO definition of anaemia only[b])				
All-cause mortality NR (N=NR)	NR	NR	uOR 2.22 (2.04, 2.42)	Anaemia significantly increases all-cause mortality P<0.001 *Heterogeneity I^2=36.5%*
CHF (adjusted estimates only)				
All-cause mortality NR (N=127,437)	NR	NR	aHR 1.46 (1.26, 1.69)	Anaemia significantly increases all-cause mortality P<0.001 *Heterogeneity NR*
EXTERNAL VALIDITY				
Generalisability				
Generalisable to an adult population with chronic heart failure.				
Applicability				
No details provided on location of included studies but a large number of studies included. Possibly applicable to the Australian setting.				
Comments				
The authors conclude that anaemia is an independent risk factor for mortality in patients with CHF. This association holds for both diastolic and systolic heart failure. The increased risk remains when sensitivity analyses are performed including only studies with the same definition of anaemia. The authors also note that the effect of anaemia on mortality declined with higher serum creatinine levels and that lower baseline Hb levels were associated with increased annual mortality rates. The authors note the generally high quality of the included studies. They also note that residual confounding in from studies in the adjusted analysis could not be ruled out and that this limits their ability to prove causality.				

ITT, intention-to-treat; CI, confidence interval; Hb, haemoglobin; Ht, haematocrit; MA, meta-analysis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; uOR, unadjusted odds ratio; WHO, World Health Organization.

[a] 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] Hb <13.0 g/dL for males and Hb <12.0 g/dL for females.

STUDY DETAILS: SR/MA				
Citation				
He S-W, Wang L-W (2009) The impact of anemia on the prognosis of chronic heart failure: a meta-analysis and systematic review. Congestive Heart Failure 15: 123–130.				
Affiliation/Source of funds				
Charles Sturt University, Australia; Weifdang Medical University, China.				
Study design	Level of evidence	Location/setting		
Systematic review of literature. Includes data from 21 prospective observational studies.	Level I (aetiology)	Various		
Intervention/risk factor	Comparator			
Anaemia (based on the WHO criteria: Hb < 13 g/dL for men and < 12 g/dL for women)	No anaemia			
Population characteristics				
Heart failure (LVEF ranged from <23% to ≥ 50% across the included studies, although most were <40); mean age ranged from 61 to 78 across the included studies.				
Length of follow-up	Outcomes measured			
Ranged from 1 to 10 years	Mortality; hospitalisation			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Good search strategy; limited to prospective observational studies; study quality assessed and 18/20 studies considered to be of high quality; characteristics results of individual studies reported; reported individual study results for adjusted analyses but did not pool results. Some errors found in this publication which have been rectified in this data extraction form.				
RESULTS				
Outcome No. trials (No. patients)	Anaemia n/N (%)	No anaemia n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
CHF				
Unadjusted analyses				
Mortality 6 studies (N=12475)	601/1790 (33.6)	2246/10685 (21.0)	uRR 1.66 (1.40, 1.96)	Anaemia significantly increases mortality risk P<0.001 *Heterogeneity 0.008*
Adjusted categorical analyses				
Komajda 2006 (N=2996) Retrospective analysis of COMET	WHO anaemia (Men Hb <13.0 g/dL; women Hb < 12.0 g/dL)	No anaemia	aRR 1.47 (1.27, 1.71)	Anaemia significantly increases mortality risk P<0.05

	Adjusted for age, gender, NYHA classification, SBP, BMI, duration of HF, LVEF, diabetes, ischaemic aetiology, serum creatinine, serum sodium, concomitant use of aspirin, anticoagulants, lipid lowering drugs.			
Anand 2005 (N=5002) Retrospective analysis of Val-HeFT	WHO anaemia (Men Hb <13.0 g/dL; women Hb < 12.0 g/dL)	No anaemia	aHR 1.21	Anaemia significantly increases mortality risk P=0.02
	Adjusted for BNP category, NYHA category, uric acid, absolute neutrophil count, LVIDd/BSA, PRA, baseline use of β-blockers, origin, age, creatinine, NE category, absolute lymphocyte count, LVEF, aldosterone, treatment.			
Ezekowitz 2003 (N=12065) Population cohort	ICD codes 280–289	No anaemia	aHR 1.34 (1.24, 1.46)	Anaemia significantly increases mortality risk P<0.05
	Adjusted for age, gender, hypertension, ischaemic heart disease, peripheral vascular disease, malignancy, chronic renal insufficiency.			
Go 2006 (N=59772) Population cohort	Hb 12.0–12.9 g/dL	Hb 13–13.9 g/dL	aHR 1.16 (1.11, 1.21)	Anaemia significantly increases mortality P<0.05
	Hb 11.0–11.9 g/dL	Hb 13–13.9 g/dL	aHR 1.50 (1.44, 1.57)	Anaemia significantly increases mortality P<0.05
	Hb 10.0–10.9 g/dL	Hb 13–13.9 g/dL	aHR 1.89 (1.80, 1.98)	Anaemia significantly increases mortality P<0.05
	Hb 9.0–9.9 g/dL	Hb 13–13.9 g/dL	aHR 2.31 (2.18, 2.45)	Anaemia significantly increases mortality P<0.05
	Hb <0.9 g/dL	Hb 13–13.9 g/dL	aHR 3.48 (3.25, 3.73)	Anaemia significantly increases mortality P<0.05
	Adjusted for GFR, age, gender, race/ethnicity, AMI, angina, other diagnosed coronary disease, coronary revascularisation, ischaemic stroke or TIA, PAD, DM, diagnosed hypertension, cancer, thyroid disease, pericarditis, chronic lung or liver disease, HIV infection, valvular heart disease, diagnosed dementia or depression, documented ventricular fibrillation or tachycardia, atrial fibrillation or flutter, left ventricular systolic function status, and use of ACE inhibitors, AIIRAs, diuretics, β-blockers, spironolactone, other direct vasodilators, calcium channel blockers, statins, other lipid lowering therapies and erythropoietin.			
Valeur 2006 (N=1731) Retrospective analysis of TRACE	WHO anaemia (Men Hb <13.0 g/dL; women Hb < 12.0 g/dL)	No anaemia	aHR 1.16 (1.01, 1.34)	Anaemia significantly increases mortality risk P<0.05
	Mild anaemia (Men Hb 12.0 - < 13.0 g/dL; women Hb 11.0 - < 12.0 g/dL)	No anaemia	aHR 1.05 (0.88, 1.25)	Mild anaemia does not increase mortality risk P≥0.05

	Moderate anaemia (Men Hb 11.0 - < 12.0 g/dL; women Hb 10.0 - < 11.0 g/dL)	No anaemia	aHR 1.20 (0.93, 1.56)	Moderate anaemia does not increase mortality risk P≥0.05
	Severe anaemia (Men Hb < 11.0 g/dL; women <10.0 g/dL)	No anaemia	aHR 1.65 (1.21, 2.25)	Severe anaemia significantly increases mortality risk P<0.05
	Adjusted for age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index and treatment with fibrinolysis and ACE inhibitors.			
Szachniewicz 2003 (N=176) Hospital cohort	Hb < 12.0 g/dL	No anaemia	aHR 2.61 (1.05, 6.47)	Anaemia significantly increases mortality P=0.04
	Adjusted for NYHA class and LVEF.			
Shamagian 2006 (N=210) Hospital cohort	WHO anaemia (Men Hb <13.0 g/dL; women Hb < 12.0 g/dL)	No anaemia	aRR 2.647 (1.308, 5.357)	Anaemia significantly increases mortality P=0.007
	Adjusted for age, ischaemic aetiology, gender, diabetes mellitus, NYHA Class, ACE inhibitors and GFR.			
Latado 2006 (N=303) Hospital cohort	WHO anaemia (Men Hb <13.0 g/dL; women Hb < 12.0 g/dL)	No anaemia	aOR 2.7 (1.47, 5.04)	Anaemia significantly increases in-hospital mortality risk P=0.002
	Adjusted for age, gender, atrial fibrillation, ischaemic cause of HF, diabetes mellitus, renal dysfunction, hyponatremia and LV systolic function.			
Newton 2006 (N=528) Hospital cohort	Men Hb <13.0 g/dL' women Hb 11.5 g/dL	No anaemia	aHR 1.415 (1.087, 1.841)	Anaemia significantly increases mortality risk P=0.010
	Adjusted for age, SBP, plasma creatinine and plasma glucose.			
Hebert 2006 (N=410) Hospital cohort	WHO anaemia (Men Hb <13.0 g/dL; women Hb < 12.0 g/dL)	No anaemia	aHR 1.64 (0.95, 2.85)	
	Men Hb <13.0 g/dL	No anaemia	aHR 2.54 (1.31, 4.93)	Anaemia significantly increases mortality P<0.05
	Women Hb < 12.0 g/dL	No anaemia	aHR 0.49 (0.16, 1.54)	
	Adjusted for age, GFR and LVEF.			

Horwich 2002[b] (N=1061) Hospital cohort	Hb <12.3	Hb > 14.8	aRR 1.861 (1.215, 2.852)	Anaemia significantly increases mortality P<0.05
	Hb 12.3–13.6	Hb > 14.8	aRR 1.369 (0.871, 2.145)	
	Hb 13.7–14.8	Hb > 14.8	aRR 1.298 (0.826, 2.039)	
	Adjusted for age, gender, BMI, left ventricular end diastolic dimension, history of hypertension, diabetes, smoking, serum sodium, albumin, creatinine and heart failure aetiology.			
Kerzner 2007[c] (N=204) Hospital cohort	Hb < 11.5	Hb > 13.4	aHR 2.3 (1.2, 4.3)	Anaemia significantly increases mortality P=0.01
	Hb 11.5–13.4	Hb > 13.4	aHR 2.0 (1.1, 3.8)	Anaemia significantly increases mortality P=0.03
Adjusted continuous analyses				
Anand 2004 (N=912) Retrospective analysis of RENAISSANCE	Baseline Hb (g/dL) as a continuous variable		aHR 0.915	A 1 g/dL increase in Hb is associated with a 8.5% reduction in risk of death P=0.021
	Adjusted for β-blockers, antiarrhythmic drugs, NYHA functional class, baseline DBP and serum creatinine concentration.			
Felker 2006 (N=4951) Hospital cohort	Hb (g/dL) as a continuous variable		aHR 1.12	A 1 g/dL decrease in Hb is associated with a 12% increase in risk of death P<0.0001
	Adjusted for age, gender, race, ejection fraction, diabetes mellitus, ischaemic aetiology, number of diseased vessels, NYHA class, inpatient status at index angiography, active smoking, Charlson Index and creatinine.			
Maggioni 2005 (N=2411) Retrospective analysis of IN-CHF	Hb (g/dL) as a continuous variable		aHR 0.903 (0.839, 0.973)	A 1 g/dL increase in Hb is associated with a 9.7% reduction in risk of death P<0.05
	Adjusted for age, gender, SBP, heart rate, third heart sound, BMI, NYHA Class, ischaemic aetiology, LVEF, creatinine, valsartan, AVE inhibitors, β-blockers and bilirubin.			
Maggioni 2005 (N= 5010) Retrospective analysis of Val-HeFT	Hb (g/dL) as a continuous variable		aHR 0.922 (0.881, 0.966)	A 1 g/dL increase in Hb is associated with a 7.8% reduction in risk of death P<0.05
	Adjusted for age, gender, SBP, heart rate, third heart sound, BMI, NYHA Class, ischaemic aetiology, LVEF, creatinine, valsartan, AVE inhibitors, β-blockers and bilirubin.			

van der Meer 2004 (N=74) Hospital cohort	Hb (g/dL) as a continuous variable	aHR 0.408 (0.219, 0.759)	A 1 g/dL increase in Hb is associated with a 58.2% reduction in risk of death P=0.005
	Adjusted for age, gender, history of hypertension, history of diabetes, aetiology of CHF, LV end-diastolic dimension, calculated GFR, sodium levels, concomitant medication and severity of CHF assessed by BNP levels, LVEF and VO_2.		
EXTERNAL VALIDITY			
Generalisability			
Generalisable to a population with heart failure.			
Applicability			
No details provided on location of included studies but a large number of studies included. Possibly applicable to the Australian setting.			
Comments			
The authors conclude that the majority of included studies suggest that all-cause mortality or hospitalisation rates are higher in patients with anaemia compared to those without anaemia, and that anaemia is an independent risk factor of both mortality and hospitalisation. They note that a number of studies showed that every 1 g/dL increase or decrease in Hb value was associated with a significantly lower or higher risk of mortality or hospitalisation. It should be noted that while this was considered to be a good quality systematic review on the basis of the quality assessment, further investigation of the data following retrieval of the individual studies revealed a number of errors. However, correction of these has not changed the overall findings of the review.			

aHRR, adjusted hazard rate ratio; ITT, intention-to-treat; CI, confidence interval; IN-CHF, Italian Network on Congestive Heart Failure registry; MA, meta-analysis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; uHRR, unadjusted hazard rate ratio; Val-HeFT, Valsartan Heart Failure Trial. .

[a] 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] 1-year mortality.

[c] < 75 years only.

STUDY DETAILS: SR/MA		
Citation		
Lindenfeld (2005) Prevalence of anemia and effects on mortality in patients with heart failure. Am Heart J 149: 391–401.		
Affiliation/Source of funds		
University of Colorado Health Sciences Center, US. Support for the literature review and preparation of the manuscript came from Amgen Inc.		
Study design	Level of evidence	Location/setting
Systematic review of literature. Includes data from 29 studies (3 Medicare populations), 6 hospital cohorts, 10 outpatient cohorts and 7 clinical research studies)	Level I-III (aetiology)	Various
Intervention/risk factor	Comparator	
Anaemia (present or Hb levels; dependant on each authors individual definition)	No anaemia (not present or different Hb levels)	

Population characteristics				
Diagnosis of heart failure; mean age varied from ~ 51 to 79 years; % male ranged from ~37% to 100%.				
Length of follow-up	Outcomes measured			
Follow-up in the 13 studies which provided data on anaemia and mortality ranged from 60 days to 3 years.	Mortality			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Good search strategy; search terms not reported. No quality assessment of individual studies included. Characteristics and results of individual studies reported. No pooling of results.				
RESULTS				
Outcome No. trials (No. patients)	Anaemia n/N (%)	No anaemia n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
HF				
Mortality 13 studies (N=NR)	NR	NR	NR	NR
Individual study results				
Kosiborod 2003 (N=2281) Medicare population cohort Follow-up 1 year	Hct as a continuous outcome		NR	A 1% decrease in Hct results in a 2% increase in mortality
McClellan 2002 (N=633) Medicare population cohort Follow-up 1 year	Hct as a continuous outcome		NR	A 1% increase in Hct results in a 1.6% decrease in mortality
Szachniewicz 2003 (N=176) Hospital cohort Follow-up mean 529 days	Hb < 12.0 g/dL	No anaemia	HR 2.61 (1.05, 6.47)	Anaemia results in a significantly increased mortality risk
Ezekowitz 2003 (N=12065) Hospital cohort Follow-up mean 573 days	Hb < 11.0 g/dL	No anaemia	HR 1.34 (1.24, 1.46)	Anaemia results in a significantly increased mortality risk
Horwich2002 (N=1061) Outpatient clinic cohort Follow-up 1 year	WHO anaemia (mean Hb < 13.0 g/dL; women < 12.0 g/dL)	No anaemia	NR	1g/dL decrease in Hb results in a 16% increase in mortality

Kalra 2003 (N=552) Outpatient clinical cohort Follow-up median 3 years	Hb < 13.0 g/dL	No anaemia	NR	No association with mortality
Golden 2002 (N=239) Outpatient clinical study Follow-up mean 23.1 months	Hct L25	No anaemia	NR	Decrease in Hct the single most powerful predictor of mortality
Bolger 2002 (N=157) Outpatient clinical study Follow-up mean 31 months	Hb < 12.1 g/dL	No anaemia	NR	1 g/dL decrease in Hb results in a 38% increase in mortality
Sharma 2004 (N=3044) Clinical trial ELITE II Follow-up median 551 days	Hb < 12.5 g/dL	No anaemia	NR	Non-linear mortality that increases above and below 14.5 g/dL
Mozaffarian 2003 (N=1130) Clinical trial PRAISE Follow-up mean 15 months	Hct ≤ 37.6%	No anaemia	NR	Hct only associated with mortality in the lowest quintile
Al-Ahmad 2001 (N=6563) Clinical trial SOLVD Follow-up mean 3.4 months	Hct ≤ 39%	No anaemia	NR	1% decrease in Hct results in a 2.7% increase in mortality
Felker 2003 (N=906) Clinical trial OPTIME-CHF Follow-up 60 days	WHO anaemia (mean Hb < 13.0 g/dL; women < 12.0 g/dL)	No anaemia	NR	1 g/dL increase in Hb results in an 11% decrease in mortality and hospitalisation
Anand 2004 (N=912) Clinical trial RENAISSANCE Follow-up mean 12.7 months	Hb < 12.0 g/dL	No anaemia	NR	1 g/dL increase in Hb results in a 15.8% decrease in mortality and hospitalisation

EXTERNAL VALIDITY
Generalisability
Generalisable to a population with heart failure.
Applicability
No details provided on location of included studies but a substantial number of studies included. Possibly applicable to the Australian setting.
Comments
The authors conclude that anaemia is associated with an increased mortality and the more severe the anaemia the higher the mortality risk. However, they note that these studies lack uniform definitions of anaemia and patient populations.

aHRR, adjusted hazard rate ratio; ITT, intention-to-treat; CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; MA, meta-analysis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; uHRR, unadjusted hazard rate ratio; WHO, World Health Organization.

[a] 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%.

Level II evidence

STUDY DETAILS: Cohort study		
Citation		
Adams et al (2009) Prospective evaluation of the association between hemoglobin concentration and quality of life in patients with heart failure. American Heart Journal 158: 965–971.		
Affiliation/Source of funds		
University of North Carolina, Chapel Hill; Case Western Reserve University, Cleveland; Detroit Medical Center, Detroit, Greater Cincinnati Cardiovascular Consultants, Cincinnati; University of Cincinnati, Cincinnati; Campbell university School of Pharmacy, Research Triangle Park; University of Maryland School of Medicine, Baltimore; Duke University School of Medicine, Durham; Loma Linda University, Loma Linda; Amgen Inc, Thousand Oaks; Emory University School of Medicine, Atlanta; Mercy Iowa City, Iowa City, US. Funded by Amgen Inc.		
Study design	Level of evidence	Location/setting
Cohort analysis of a prospective registry (STAMINA-HFP)	Level II	Outpatient/US
Risk factor/s assessed	Potential confounding variables measured	
Hb levels	Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	
Population characteristics (including size)		
Randomly selected outpatients with heart failure recruited from selected heart failure specialty practices and community-based cardiology practices with an interest in heart failure; mean age ~ 63 years, female ~ 41%.		

Length of follow-up	Outcomes measured
12 months	Quality of life (Kansas City Cardiomyopathy Questionnaire[2] and the Minnesota Living with Heart Failure Questionnaire[3]).

Method of analysis
Regression models were used to adjust for a large number of potential confounding variables.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good Description: Cohort analysis of data from a prospective registry; two populations analysed – (1) those with baseline data and (2) those with baseline and follow-up data; the characteristics of the patients in these two groups were compared with those with no qoL data at baseline and shown to be similar; assessment of QoL conducted by phone by trained investigators who were unaware of Hb level; follow-up up to 12 months.
RESULTS

Population	With risk factor		Without risk factor	
Available	1612			
Analysed	1362			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
KCCQ-Functional (N=826) Group 1	Categories of Hb predominantly from 11 to 14 g/dL		MD 1.1 (0.4, 1.8)	*Higher baseline Hb concentration is significantly associated with higher (improved) KCCQ-functional scores* P=0.001
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.				
KCCQ-Symptoms (N=826) Group 1	Categories of Hb predominantly from 11 to 14 g/dL		MD 1.5 (0.7, 2.3)	*Higher baseline Hb concentration is significantly associated with higher (improved) KCCQ-symptoms scores* P<0.001
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.				

[2] Green et al (2000) Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 35: 1245-1255.

[3] Rector et al (1987) Patients' self-assessment of their congestive heart failure. Part 2: content, reliability and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. Heart Failure 3: 198-209.

KCCQ-Clinical (N=826) Group 1	Categories of Hb predominantly from 11 to 14 g/dL	MD 0.9 (0.3, 1.6)	*Higher baseline Hb concentration is significantly associated with higher (improved) KCCQ-clinical scores* P=0.006
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
MLHFQ-Physical (N=up to 826) Group 1	Categories of Hb predominantly from 11 to 14 g/dL	MD -0.4 (-0.8, -0.04)	*Higher baseline Hb concentration is significantly associated with lower (improved) MLHFQ-physical scores* P=0.029
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
MLHFQ-Emotional (N=up to 826) Group 1	Categories of Hb predominantly from 11 to 14 g/dL	MD -0.2 (-0.4, 0.06)	*Higher baseline Hb concentration is not significantly associated with MLHFQ-emotional scores* P=0.14
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
MLHFQ-Summary (N=up to 826) Group 1	Categories of Hb predominantly from 11 to 14 g/dL	MD -0.7 (-1.5, 0.1)	*Higher baseline Hb concentration is not significantly associated with MLHFQ-summary scores* P=0.092
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Outcome (Continuous)	Risk factor definition	Risk estimate (95% CI)	Significance P-value
KCCQ-Functional (N= 536) Group 2	1 g/dL change in Hb through 12 months	MD 1.3 (0.7, 1.8)	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P<0.001
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			

KCCQ-Symptoms (N= 536) Group 2	1 g/dL change in Hb through 12 months	MD 1.5 (0.8, 2.1)	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P<0.001
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
KCCQ-Clinical (N= 536) Group 2	1 g/dL change in Hb through 12 months	MD 1.2 (0.7, 1.7)	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P<0.001
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
MLHFQ-Physical (N=up to 536) Group 2	1 g/dL change in Hb through 12 months	MD -0.5 (-0.8, -0.1)	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P=0.004
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
MLHFQ-Emotional (N=up to 536) Group 2	1 g/dL change in Hb through 12 months	MD -0.1 (-0.3, 0.1)	*A 1 g/dL change in Hb over 12 months is not significantly associated with a change in QoL* P=0.389
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
MLHFQ-Summary (N=up to 536) Group 2	1 g/dL change in Hb through 12 months	MD -1.1 (-1.7, -0.4)	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P=0.002
Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population with heart failure.			
Applicability			
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.			

Comments
The authors conclude that they are the "first to demonstrate a significant, direct relationship between hemoglobin concentration and quality of life in an unselected population of outpatients with chronic heart failure. Patients with reduced hemoglobin had poorer health-related quality of life than patients with higher hemoglobin." The authors note a number of limitations of their study including (i) that they cannot establish a causal effect based on their study; (ii) that different causes of haemoglobin reduction may have been associated directly with QoL; (iii) that data was missing in some patients and that incomplete sampling may have biased the results; and (v) that site selection was not random and may have biased the results.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DBP, diastolic blood pressure; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MD, mean difference; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; SBP, spontaneous bacterial peritonitis; QoL, quality of life; US, United States of America

STUDY DETAILS: Cohort study		
Citation		
Anand et al (2005) Anemia and change in haemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation 112: 1121–1127.		
Affiliation/Source of funds		
VA Medical Center, Minneapolis, Minn, US; Novartis Pharmaceuticals Corporation, East Hanover, NJ, US; ANMCO Research Center, Florence, Italy; Ospedale Clivile, Udine, Italy; Instituto "Mario Negri", Milano, Italy. Funded by Novartis Pharmaceuticals AG, Basel, Switzerland.		
Study design	Level of evidence	Location/setting
Cohort analysis of a double-blind RCT (Val-HeFT) comparing valsartan with placebo	Level II	Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Spain, Sweden, UK, US
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (WHO criteria and haemoglobin measured as change from baseline quartiles and as a continuous outcome)	Adjusted for variables shown to be independently associated with anaemia at baseline: BNP category, NYHA category, uric acid, absolute neutrophil count, LVIDd/BSA, PRA, baseline use of β-blockers, origin (ischaemic vs non-ischaemic), age, creatinine, NE, category, absolute, lymphocyte count, LVEF, aldosterone, treatment (valsartan vs placebo).	
Population characteristics (including size)		
Chronic heart failure (≥ 18 years, heart failure for at least 3 months prior to screening, NYHA Class II-IV, clinically stable, fixed dose regimen of ACEI, diuretic, digoxin or β-blocker for at least 2 weeks, documented LVEF < 40% and LV dilatation with an echocardiographically measured short axis internal dimension at end diastole greater than 2.9 cm per square metre of body surface area). No anaemia vs anaemia: age 62 vs 66; female 20% vs 21%; White 92% vs 83%; ischaemic origin 44% vs 39%; diabetes 23% vs 34%. N=5002		
Length of follow-up	Outcomes measured	
24 months	Mortality; morbid event (death, sudden death with resuscitation, hospitalisation for heart failure or administration of IV inotropic or vasodilator drugs for ≥ 4 hours without hospitalisation)	

Method of analysis				
Logistic regression used to identify potential confounding variables. Cox proportional-hazards used to relate anemia, change in haemoglobin and other variables to mortality.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Re-analysis of data from a double-blind RCT; a proportion of the patients included in original RCT (n=5010) not included in re-analysis (may be N=5002) but that is somewhat unclear; reasons for exclusion not stated); mortality is an objective outcome; mean 23 months follow-up; treatment with intervention/control did not affect results (adjusted for in analysis).				
RESULTS				
Population	N			
Available	5010			
Analysed	5002		1145	
Outcome (categorical)	Risk factor	No risk factor	Risk estimate (95% CI)	Significance P-value
Mortality N=5002	Anaemia (WHO criteria)	No anaemia	HR 1.21	*Anaemia is a significant independent risk factor for 2-year mortality* P=0.02
Mortality N=1499	- 1.64 g/dL change (range -6.3 to -0.9)	0.14 g/dL change (range -0.1 to 0.4)	HR 1.6 (1.16, 2.2)	*A substantial reduction in haemoglobin from baseline is significantly associated with an increased risk of mortality* P=0.004
Mortality N=1532	-0.48 g/dL change (range -0.8 to -0.2)	0.14 g/dL change (range -0.1 to 0.4)	HR 1.10 (0.79, 1.55)	*A small reduction in haemoglobin from baseline is not associated with an increased risk of mortality* P=0.57
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value
Mortality in patients with anaemia at baseline who survived 12 months N=668	An increase of Hb of 1 g/dL		HR 0.78 (0.65, 0.93)	*A 1 g/dL increase of Hb over 12 months in patients with anaemia at baseline significantly reduces the risk of 12-month mortality* P=NR

Mortality in patients without anaemia at baseline who survived 12 months N=2424	An increase of Hb of 1 g/dL	HR 0.79 (0.71, 0.89)	*A 1 g/dL increase of Hb over 12 months in patients without anaemia at baseline significantly reduces the risk of 12-month mortality* P=NR
EXTERNAL VALIDITY			
Generalisability			
This evidence is generalisable to a population with chronic heart failure.			
Applicability			
This evidence was conducted in a large number of patients in various countries including Australia. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors conclude that "changes in Hgb over 12 months were inversely associated with subsequent risk of mortality and morbidity, independent of the effects of baseline anaemia and other important predictors".			

ACEI, angiotensin-converting enzyme inhibitor; BNP, Brain-type natriuretic peptide; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; Hgb, haemoglobin; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd/BSA, left ventricular internal diastolic diameter/body surface area; NE, norepinephrine; NR, not reported; NYHA, New York Heart Association; PRA, plasma renin activity; RCT, randomised controlled trial; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Anker et al (2009) Prevalence, incidence and prognostic value of anaemia in patients after an acute myocardial infarction: data from the OPTIMAAL trial. European Heart Journal 30: 1331–1339.		
Affiliation/Source of funds		
Department of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany; Department of Clinical Cardiology, NHLI London, UK; Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; Department of Academic cardiology, Castle Hill Hospital, Hull, UK; Merck Research laboratories, West Point, PA, US; Department of Cardiology, Rishospitalet, Oslo, Norway; Cardiac Department, Military Hospital, Wroclaw, Poland; Stavanger University Hospital, University of Bergen, Bergen, Norway.		
Study design	Level of evidence	Location/setting
Re-analysis of a double-blind RCT comparing losartan and captopril	Level II	Denmark, Finland, Germany, Ireland, Norway, Sweden, UK
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (categorical and continuous)	Age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.	

Population characteristics (including size)				
Diagnosis of acute myocardial infarction and signs or symptoms of heart failure during the acute phase suggested by one or more of the following: treatment with diuretic or intravenous vasodilator therapy for heart failure; pulmonary rales; third heart sound; persistent sinus tachycardia (≥ 100 bpm); radiographic evidence of pulmonary congestion. Also, AMI and a LVEF < 35% or a left-ventricular end-diastolic dimension or greater than 65 mm (optional) and/or a new Q-wave anterior wall AMI, or any reinfarction with previous pathological Q-waves in the anterior wall. Mean age 67.4; female 28.4%; BMI 26.6. N=5477				
Length of follow-up	Outcomes measured			
Median 3 years	*All-cause death*; cardiovascular hospitalisation; CHF hospitalisation; any hospitalisation; all-cause death or CHF hospitalisation; *sudden cardiac death; death due to progressive heart failure*			
Method of analysis				
Cox-proportional hazards analysis was performed to assess the association between baseline variables and endpoints. Factors which are known to be of prognostic value in heart failure were included in a multivariable model (see above).				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Re-analysis of a double-blind RCT (OPTIMAAL); 91.5% of 5477 randomised patients who had baseline Hb measurement were included in the analysis (no discussion of characteristics of missing patients); results adjusted for a large number of potential confounders.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	5477			
Analysed	5010			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All-cause mortality N=5010	Anaemia (WHO)	No anaemia	HR 1.35 (1.16, 1.56)	*Anaemia is a significant independent risk factor for all-cause mortality* P<0.0001
Sudden cardiac death N=5010	Anaemia (WHO)	No anaemia	HR 1.14 (0.89, 1.48)	*Anaemia is not an independent risk factor for sudden cardiac death* P=0.303
Death due to progressive heart failure N=5010	Anaemia (WHO)	No anaemia	HR 1.55 (1.13, 2.13)	*Anaemia is a significant independent risk factor for death due to progressive heart failure* P=0.006

Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
All-cause death N=5010	Increase in Hb of 1 SD	HR 0.88 (0.83, 0.93)	*A one SD increase in Hb results in a significantly decreased risk of all-cause mortality* P<0.001
Sudden cardiac death N=5010	Increase in Hb of 1 SD	HR 0.86 (0.80, 1.03)	*A one SD increase in Hb does not result in a significantly decreased risk of sudden cardiac death* P=0.141
Death due to progressive heart failure N=5010	Increase in Hb of 1 SD	HR 0.80 (0.69, 0.94)	*A one SD increase in Hb results in a significantly decreased risk of death due to progressive heart failure* P=0.006
All-cause mortality in patients alive at 12 months N=3921	12-month change in Hb of 1 SD	HR 0.73 (0.63, 0.85)	*A 12-month change of Hb of 1 SD results in a significantly decreased risk of all-cause mortality* *P<0.001*
All-cause mortality in patients alive at 12 months N=3921	12-month increase in Hb of 1 SD	HR 0.67 (0.51, 0.81)	*A 12-month increase of Hb of 1 SD results in a significantly decreased risk of all-cause mortality* *P<0.01*
All-cause mortality in patients alive at 12 months N=3921	12-month decrease in Hb of 1 SD	HR 1.27 (1.00, 1.60)	*A 12-month decrease of Hb of 1 SD results in a significantly increased risk of all-cause mortality* *P=0.05*
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of patients with an acute myocardial infarction complicated by heart failure.			
Applicability			
This study was conducted in a large number of subjects in a number of countries and is likely to be applicable to the Australian setting.			
Comments			
The authors conclude that "in patients with complicated AMIs, anaemia on admission and/or reductions in haemoglobin during follow up are independent risk factors for mortality and hospitalisation".			

AMI, acute myocardial infarction; BMI, body mass index; bpm; beats per minute; CHF, congestive heart failure; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; RCT, randomised controlled trial; SD, standard deviation; UK, United Kingdom; WHO, World Health Organisation.

STUDY DETAILS: Cohort study				
Citation				
Baggish et al (2007) Hemoglobin and N-terminal pro-brain natriuretic peptide: independent and synergistic predictors of mortality in patients with acute heart failure. Results from the International Collaborative of NT-proBNP (ICON) study. Clinica Chimica Acta 381: 145–150.				
Affiliation/Source of funds				
Massachusetts General Hospital, Boston, US; University Hospital, Maastricht, The Netherlands; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand.				
Study design	Level of evidence		Location/setting	
Prospective hospital registry	Level II		US, The Netherlands, Spain, New Zealand/hospital	
Risk factor/s assessed		Potential confounding variables measured		
Anaemia (WHO), NT-pro-BNP		Age, hypertension, coronary artery disease, loop diuretic use, paroxysmal nocturnal dyspnoea, fever, ECG left bundle branch block, creatinine, creatinine clearance, troponin, NT-pro-BNP; NYHA class, signs of haemodilution.		
Population characteristics (including size)				
Community-based patients diagnosed with acute heart failure; mean age ~ 75, male ~ 51.5%. N=690				
Length of follow-up		Outcomes measured		
60 days		60-day mortality		
Method of analysis				
Independent predictors of 60-day mortality were identified using forward stepwise logistic regression.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Combined data from a number of published and unpublished prospective hospital registries; of 720 subjects diagnosed with acute HF, 96% had available haemoglobin data (no details on characteristics of those without Hb measurement); analysis adjusted for a large number of potential confounders; mortality assessed by hospital records, death certificate and telephone follow-up with physician; 60-day follow-up.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	720			
Analysed	305		385	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
60-day mortality (N=690)	Anaemia (WHO)	No anaemia	OR 1.72 (1.05, 2.80)	*Anaemia is an independent risk factor for 60-day mortality* P=0.032
EXTERNAL VALIDITY				

Generalisability
The results of this study are generalisable to a population with acute heart failure.
Applicability
This study was conducted in the US, The Netherlands, Spain and New Zealand. The results of this study are likely to be applicable to the Australian setting. ,
Comments
As well as anaemia, other independent risk factors for 60-day mortality identified were NT-pro-BNP (OR 2.32; p=0.002); creatinine clearance (OR 0.98; p=0.003); fever (OR 2.65; p=0.03); and age (OR 1.28; p=0.049).

CI, confidence interval; ECG, electrocardiograph; Hb, haemoglobin; HF, heart failure; NT-pro-BNP, N-terminal-pro-Brain-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Ceresa et al (2005) Anemia in chronic heart failure patients: comparison between invasive and non-invasive prognostic markers. Monaldi Arch Chest Dis 64: 124–133.		
Affiliation/Source of funds		
Instituto Scientifico di Montescano, Italy. Funded by Ministerio della Salute.		
Study design	Level of evidence	Location/setting
Prospective hospital-based cohort study	Level II	Hospital/Italy
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (< 12 g/dL Hb)	RAP, sodium, LVEF, mitral regurgitation, NYHA class and possibly others.	
Population characteristics (including size)		
Adults with CHF caused by ischaemia, idiopathic dilated cardiomyopathy or other disease (eg, hypertension, valvular disease) entering a heart transplant programme; mean age 53 years, male 85%. N=980		
Length of follow-up	Outcomes measured	
3 years	Cardiac death (those due to heart failure or sudden death) or urgent heart transplant (assumed that these patients would have died without transplant).	
Method of analysis		
Separate multivariate analyses carried out including non-invasive parameters and non-invasive and invasive parameters. Only all parameter analysis included here.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: Prospective hospital-based cohort study; unclear if all available patients included (methods sections states consecutive patients included but discussion notes selected patients); unclear exactly what variables were considered in the multivariate analysis; not stated how follow-up occurred; 3-year follow-up.		
RESULTS		

Population	With risk factor		Without risk factor	
Available	NR			
Analysed	187		793	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Cardiac death or urgent heart transplant (N=980)	Anaemia (Hb < 12 g/dL)	No anaemia	NR	*Anaemia is not an independent predictor of cardiac mortality/urgent heart transplant* P=NR
EXTERNAL VALIDITY				
Generalisability				
This study was conducted in patients with chronic heart failure entering a heart transplant programme.				
Applicability				
This study was conducted in Italy. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that the relationship between anaemia and mortality is independent of other simple non-invasive prognostic models. However, when invasive parameters were included in the model, anaemia was no longer an independent predictor. The authors note a number of limitations of their study including the inclusion of selective patients who were entering a heart transplant programme; the under-representation of elderly patients and women; and the fact that the aetiology of anaemia was not studied.				

CHF, congestive heart failure; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association; RAP, right atrial pressure.

STUDY DETAILS: Cohort study		
Citation		
Felker et al (2003) Usefulness of anemia as a predictor of death and rehospitalisation in patients with decompensated heart failure. Am J Cardiol 92: 625–628.		
Affiliation/Source of funds		
Duke Clinical Research Institute, Durham, NC, US; University of North Carolina-Chapel Hill, Chapel Hill, NC, US; Northwestern University, Chicago, IL, US. The OPTIME-CHF trial was funded by Sanofi-Syntheabo but the re-analysis presented in this publication was funded independently by Duke Clinical Research Institute.		
Study design	Level of evidence	Location/setting
Re-analysis of a double-blind, placebo-controlled RCT.	Level II	US

Risk factor/s assessed	Potential confounding variables measured
Haemoglobin as a continuous outcome	41 candidate variables that reflected demographics, cardiac history, co-morbid conditions, bedside assessment, and laboratory studies; to adjust for varying degrees of volume overload, variables assessed included presence of increased jugular venous pressure, peripheral oedema or a third heart sound.
Population characteristics (including size)	

Patients with systolic dysfunction and exacerbations of heart failure: ≥ 18 years and demonstrated LVEF < 40%. Mean age ~65, male ~ 66%, Caucasian ~65%. N=906			
Length of follow-up	Outcomes measured		
60 days	Primary: number of days hospitalised for cardiovascular causes within 60 days of study drug infusion Secondary: 60-day mortality rate and composite of death or rehospitalisation		
Method of analysis			
Multivariable Cox proportional hazards analysis was used to adjust for differences between groups with respect to both the primary end point and 60-day mortality rate.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Good Description: Re-analysis of a double-blind RCT; 95% of randomised subjects had baseline Hb measurement and 60-day follow-up was 99%; wide range of variables considered for inclusion in multivariable analysis; mortality a secondary outcome of the RCT.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	949		
Analysed	906 (Hb as a continuous outcome)		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
60-day mortality N=906	1 g/dl increase in Hb	NR	*There was no significant decrease in mortality associated with a 1 g/dL increase in Hb* P<0.05
EXTERNAL VALIDITY			
Generalisability			
Generalisable to a population of patients with systolic dysfunction and exacerbation of heart failure.			
Applicability			
Conducted in the US so likely to be applicable to the Australian setting.			
Comments			
While the multivariate analysis of 60-day mortality showed no significant relationship between increase in haemoglobin and mortality, the multivariable analysis did show a significant relationship between a 1g/dL increase in haemoglobin and death or rehospitalisation as a composite endpoint (OR 0.89; 0.82, 0.97; p<0.001).			

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; LVEF, left ventricular ejection fraction; NR, not reported; RCT, randomised controlled trial; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Garty et al (2007) The management, early and one-year outcome in hospitalized patients with heart failure: a national heart failure survey in Israel – HFSIS 2003. IMAJ 9: 227–233.		
Affiliation/Source of funds		
Rabin Medical Center, Petah Tikva, Israel; Hillel Yaffe Medical Center, Hadera, Israel; Bikur Holim Hospital, Jerusalem, Israel; Soroka University Hospital, Beer Sheva, Israel; Lady Davis Carmel Medical Center, Haifa, Israel; Sheba Medical Center and Israel Center for Disease Control, Ministry of Health, Tel Hashomer, Israel; Kaplan Medical Center, Rehovot, Israel. This study was supported by the Israel Center for Disease Control, the Israeli Medical Association and the following companies: Teva, Pfeizer, Merck Sharpe Dohme, Aventis, Medtronic, Dexxon, Guidant (Levant), Medisson, Neopharm, Novartis and Schering-Plough.		
Study design	Level of evidence	Location/setting
Prospective observational survey with up to 1-year follow-up	Level II	Israel
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (Hb ≤ 12 g/dL) + others	Gender, age, hypertension, diabetes mellitus, dyslipidaemia, obesity, current smoking, coronary artery disease, acute coronary syndrome, valvular heart disease, cardiomyopathy (non-ischaemic), atrial fibrillation, renal failure (creatinine ≥ 1.5 mg/dL), chronic obstructive pulmonary disorder, stroke/transient ischaemic attack, various treatments.	
Population characteristics (including size)		
Heart failure patients with stages B-D[a] according to ACC/AHA definitions, hospitalised in Israeli public hospitals between March and April 2003.		
Length of follow-up	Outcomes measured	
1 year	In hospital and 1-year mortality	
Method of analysis		
Multivariate stepwise logistic regression analyses (SAS LOGISTIC procedure) were performed to examine variables independently associated with in-hospital and 1-year mortality		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Prospective survey of all public hospitals in Israel between March to April 2007 with up to 1 year follow-up of mortality; a large number of risk factors assessed of which anaemia was just one; all subjects included in analyses; adjusted for potential confounders using multivariate analysis; mortality data collected via Israeli registry.		
RESULTS		

Population	With risk factor	Without risk factor
Available	2026	2076
Analysed	2026	2076

Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
In-hospital mortality N=4102	Anaemia (Hb ≤ 12 g/dL)	No anaemia	NR	*There is no significant relationship between anaemia and in-hospital mortality* P≥0.05
1-year mortality N=4102	Anaemia (Hb ≤ 12 g/dL)	No anaemia	OR 1.50 (1.29, 1.75)	There is a significant relationship between anaemia and 1-year mortality P<0.05
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of patients hospitalised with mild to severe heart failure.				
Applicability				
This study was conducted in Israel so likely to be applicable to the Australian setting.				
Comments				
Apart from anaemia a large number of variables were shown to be significantly associated with 1-year mortality (either favourably or not favourably); these included: NYHA III-IV, renal failure, stroke, age, COPD, atrial fibrillation, hypertension, CCU/CARD, ACEI, ARB, β-blocker, diuretics, spironolactone and digoxin. Anaemia had the third highest risk after NYHA III-IV (OR 2.07) and renal failure (OR 1.79).				

ACC, American College of Cardiology; ACEI, angiotensin converting enzyme-inhibitor; AHA, American Heart Association; CARD, cardiology unit; CCU, coronary care unit; CI, confidence interval; COPD, chronic obstructive pulmonary disease; dL, decilitre; g, grams; Hb, haemoglobin; NR, not reported; NYHA, New York Heart Association; OR, odds ratio.

[a] A: patients at high risk of developing heart failure, but without structural heart disease of heart failure symptoms; B: patients with structural heart disease but without heart failure symptoms; C: patients with structural heart disease with prior or current symptoms of heart failure; D: refractor heart failure patients who require specialised interventions.

STUDY DETAILS: Cohort study		
Citation		
Hamaguchi et al (2009) Anaemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan: a report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circulation Journal 73: 1901–1908.		
Affiliation/Source of funds		
Hokkaido University Graduate School of Medicine, Sapporo, Japan; International Medical Center of Japan, Tokyo, Japan; Futsukaichi Saiseikai Hospital, Chikusino, Japan. The JCARE-CARD was supported by the Japanese Circulation Society and the Japanese Society of Heart Failure. This study was supported by grants from the Japanese Ministry of Health, Labor and Welfare, the Japan Heart Foundation and Japan Arteriosclerosis Prevention Fund.		
Study design	Level of evidence	Location/setting
Prospective cohort	Level II	Japan (multicentre)

Risk factor/s assessed	Potential confounding variables measured
Anaemia (quartiles)	Demographic (age, sex, BMI), causes of heart failure (ischaemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricaemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge and medication use (ACEI, ARB, β-blocker, digitalis, Ca channel blocker, nitrates, antiarrhythmic, warfarin).
Population characteristics (including size)	
Patients hospitalised due to worsening heart failure as the primary cause of admission. Mean age 71.5, male 58.1%, BMI 22.2 kg/m2, ischaemic heart failure 32.8%, valvular disease 28.9%.	
Length of follow-up	Outcomes measured
Mean 2.4 years	All-cause death, cardiac-cause death, rehospitalisation, all-cause death or rehospitalisation
Method of analysis	
Baseline clinical variables, treatment factors and data about the severity of heart failure at discharge were used in developing the post-discharge Cox proportional hazards models.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: Prospective cohort registry with 2.4 years follow-up; large proportion of potentially eligible subjects not included in analysis (2675 eligible, 1960 had discharge Hb measurement and only 1582 of these followed up; analysis considered a large number of potential confounders; patients surveyed after at least 1 year for outcome status.	

RESULTS				
Population	With risk factor		Without risk factor	
Available	1448		512	
Analysed	1160		422	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All-cause mortality N=777	Discharge Hb < 10.1 g/dL	Discharge Hb ≥ 13.7 g/dL	HR 1.963 (1.300, 2.963)	*Moderate-severe anaemia (Hb < 10.1 g/dL) is an independent risk factor for all-cause mortality compared with no anaemia (Hb ≥ 13.7 g/dL)* P<0.05
All-cause mortality N=823	Discharge Hb 10.1–11.9 g/dL	Discharge Hb ≥ 13.7 g/dL	HR 1.606 (1.067, 2.417)	*Mild-moderate anaemia (Hb 10.1–11.9 g/dL) is an independent risk factor for all-cause mortality compared with no anaemia (Hb ≥ 13.7 g/dL)* P<0.05

All-cause mortality N=826	Discharge Hb 12.0–13.6 g/dL	Discharge Hb ≥ 13.7 g/dL	HR 1.315 (0.858, 2.016)	*Very mild anaemia (Hb 12.0–13.6 g/dL) is not an independent risk factor for all-cause mortality compared with no anaemia (Hb ≥ 13.7 g/dL)* P≥0.05
Cardiac death N=777	Discharge Hb < 10.1 g/dL	Discharge Hb ≥ 13.7 g/dL	HR 2.155 (1.308, 3.548)	*Moderate-severe anaemia (Hb < 10.1 g/dL) is an independent risk factor for cardiac death compared with no anaemia (Hb ≥ 13.7 g/dL)* P<0.05
Cardiac death N=823	Discharge Hb < 10.1–11.9 g/dL	Discharge Hb ≥ 13.7 g/dL	HR 1.706 (1.039, 2.800)	*Mild-moderate anaemia (Hb 10.1–11.9 g/dL) is an independent risk factor for cardiac death compared with no anaemia (Hb ≥ 13.7 g/dL)* P<0.05
Cardiac death N=826	Discharge Hb < 12.0–13.6 g/dL	Discharge Hb ≥ 13.7 g/dL	HR 1.39 (0.832, 2.324)	*Very mild anaemia (Hb 12.0–13.6 g/dL) is not an independent risk factor for cardiac death compared with no anaemia (Hb ≥ 13.7 g/dL)* P≥0.05
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a broad population hospitalised due to worsening heart failure (the authors note this is a broader population that many other studies as no additional exclusion criteria included).				
Applicability				
Study conducted at a large number of hospitals in Japan so may be applicable to the Australian setting.				
Comments				
The authors conclude that lower haemoglobin was independently associated with long term outcomes (including all-cause mortality and cardiac death) in patients hospitalised with heart failure. The authors note that the effects of haemodilution on haemoglobin levels could not be excluded, particularly in the population hospitalised with congestion.				

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, Brain-type natriuretic peptide; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

STUDY DETAILS: Cohort study			
Citation			
Ingle et al (2007) Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. European Heart Journal 28: 560–568.			
Affiliation/Source of funds			
Leeds Metropolitan University, Beckett's Park Campus, Leeds, UK; University of Hull, Castle Hill Hospital, Cottingham Kingston-upon-Hull, UK. No funding.			
Study design	Level of evidence	Location/setting	
Prospective cohort	Level II	UK (single community clinic)	
Risk factor/s assessed	Potential confounding variables measured		
6-MWT and perceived symptom severity (haemoglobin as a continuous variable assessed also).	Gender, age, BMI, NYHA class, LVSD, 6-MWT, sodium, potassium, urea, creatinine, LVEF, SBP, HR, QRS duration, log NT-proBNP, AF, angina, diabetes, ACEIs, β-blockers, loop diuretics, ankle swelling, SOB, fatigue.		
Population characteristics (including size)			
Older patients with chronic heart failure. Patients referred to local community clinic with signs of breathlessness. Heart failure was defined as current symptoms of heart failure, or a history of symptoms controlled by medication, due to cardiac dysfunction and in the absence of any more likely cause. N=1592 Age 74, male 60%, BMI 27.5.			
Length of follow-up	Outcomes measured		
In surviving patients (76.7%) median follow-up was 36.6 months.	All-cause mortality		
Method of analysis			
Cox regression models were used to develop predictor models for all-cause mortality using all baseline variables.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Prospective cohort from a local community clinic; unclear whether all potentially eligible subjects were included in the analysis; multivariate analysis conducted adjusting for a wide range of variables; no details on how mortality data collected.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	NR		
Analysed	1592		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value

All-cause mortality N=1592	Hb 1 g/dL increase	HR 0.829 (0.808, 0.850)	*A 1 g/dL increase in Hb is significantly associated with a 17.1% reduction in all-cause mortality risk* P<0.05
EXTERNAL VALIDITY			
Generalisability			
The results of this study are applicable to patients in the community with chronic heart failure.			
Applicability			
The study was conducted at a community clinic in the UK so is likely to be applicable to the Australian setting.			
Comments			
While the study was focussed on 6-MWT and self-perceived symptom severity as risk factors for mortality in older patients with chronic heart failure, haemoglobin was also identified as an independent predictor. Other variables shown to be independently associated with mortality included β-blocker use and elevates log NT-proBNP.			

6-MWT, six minute walk test; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; BMI, body mass index; BNP, Brain-type natriuretic peptide; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NR, not reported; NT-proBNP, N-terminal-pro-Brain-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SOB, signs of breathlessness; UK, United Kingdom.

STUDY DETAILS: Cohort study		
Citation		
Kalra et al (2003) Haemoglobin concentration and prognosis in new cases of heart failure. Lancet 362: 211–212.		
Affiliation/Source of funds		
Imperial College School of Medicine, London, UK; London School of Hygiene and Tropical medicine, London, UK.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	Hospital/UK
Risk factor/s assessed	Potential confounding variables measured	
Hb concentration	Age, DBP, creatinine, NYHA class, left-ventricular systolic function.	
Population characteristics (including size)		
Adults with newly diagnosed heart failure; age ~ 76, male ~ 54%. N=552		
Length of follow-up	Outcomes measured	
Mean 3.0 years	Survival	
Method of analysis		
Multivariate analysis conducted using Cox's proportional hazards method.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Fair Description: Prospective cohort study; out of 552 potentially eligible subjects, 531 (96.2%) had haemoglobin values available at presentation and were included in the analysis; analyses were adjusted for a number of potential confounding variables; mortality data collected via notification from the Office of National statistics; follow-up median 3 years.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	552		
Analysed	531		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Survival (N=531)	Hb increase (1 g/dL)	HR 0.98 (0.92, 1.04)	*A 1 g/dL increase in Hb is <u>not</u> independently associated with a change in survival.* P=0.54
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population with newly diagnosed heart failure.			
Applicability			
This study was conducted in the UK. The results of this study are likely to be applicable to the Australian setting.			
Comments			
Hb was an independent predictor of survival in the univariate analysis but not the multivariate analysis. The authors conclude that "the adverse effects of anaemia on survival might be a consequence of chronic heart failure rather than a separate process causing disease progression". However, they also note that "haemoglobin might contribute independently to adverse prognosis and disease progression later in disease progression". Variable shown in this analysis to be independently associated with survival included increase in age (10 years), increase in serum creatinine (10 mmol/L), NYHA class (IV vs II/III) and severely impaired left ventricular systolic function.			

CI, confidence interval; DBP, diastolic blood pressure; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; NYHA, New York Heart Association; UK, United Kingdom.

STUDY DETAILS: Cohort study		
Citation		
Komajda et al (2006) The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. European Heart Journal 27:1440–1446.		
Affiliation/Source of funds		
Université Pierre et Marie Curie, Paris, France; Charité Campus Virchow-Klinikum, Berlin, Germany; Imperial College, London, UK; Nottingham Clinical Research Group, Nottingham, UK; Università di Brescia, Trieste, Italy; Ospedale di Cattinara, Trieste, Italy; Sticares Cardiovascular Research Foundation, Rhoon, The Netherlands; F. Hoffman-La Roche Ltd, Basel, Switzerland; Sahlgrenska University Hospital/Östra, Göteborg, Sweden; University of Hull, Kingston-upon-Hull, UK. Study supported by F. Hoffman-La Roche Ltd.		
Study design	Level of evidence	Location/setting

Re-analysis of a double-blind RCT	Level II	Multicentre (Austria, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Norway, Portugal, Sweden, Switzerland, UK)

Risk factor/s assessed	Potential confounding variables measured
Anaemia (WHO and other categories); change in Hb over time	Randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.

Population characteristics (including size)
Chronic heart failure: NYHA class II-IV, optimal background therapy with diuretics and ACEIs, LVEF < 35% and a previous admission for a cardiovascular reason. N=2996

Length of follow-up	Outcomes measured
Median 58 months (IQR 54–64 months)	All-cause mortality, all-cause hospitalisation, death or hospitalisation, heart failure hospitalisation, death or hospitalisation for worsening heart failure.

Method of analysis
To assess the multivariable significance of anaemia, a multivariable model was generated based on 14 clinically important baseline characteristics and randomised therapy (see above).
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good. Description: Re-analysis of the double-blind COMET RCT; only 2.7% (406/14,890) of Hb measurements missing; authors note no interpolation or extrapolation o9f missing values was carried out and patients included as far as the data allowed; adjusted analysis including a large number of potential confounding variables, including randomised treatment; due to multiple testing, p<0.01 considered significant; ~ 5 years follow-up.
RESULTS

Population	With risk factor		Without risk factor	
Available	3029			
Analysed	476 (WHO anaemia)		2520	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value **(Note: α = 0.01)**
All-cause mortality N=2996	Anaemia (WHO)	No anaemia	RR 1.47 (1.27, 1.71)	*Anaemia is an independent risk factor for all-cause mortality* P<0.001
All-cause mortality N=929	Severe anaemia (Hb < 11.5 g/dL male or <10.5 g/dL female)	Normal Hb (Hb 14.0–15.0 g/dL male or 13.0–14.0 g/dL female)	RR 1.558 (1.145, 2.121)	Severe anaemia is an independent risk factor for all-cause mortality compared with normal Hb P=0.0048

All-cause mortality N=1206	Moderate anaemia (Hb 11.5–13.0 g/dL male or 10.5–12.0 g/dL female)	Normal Hb (Hb 14.0–15.0 g/dL male or 13.0–14.0 g/dL female)	RR 1.405 (1.16, 1.703)	Moderate anaemia is an independent risk factor for all-cause mortality compared with normal Hb P<0.001
All-cause mortality N=1463	No anemia (Hb 13.0–14.0 g/dL male or 12.0–13.0 g/dL female)	Normal Hb (Hb 14.0–15.0 g/dL male or 13.0–14.0 g/dL female)	RR 0.942 (0.783, 1.134)	No anaemia is not an independent risk factor for all-cause mortality compared with normal Hb P=0.529
All-cause mortality N=NR	Δ Hb ≤ 3 g/dL	Δ Hb >0–1 g/dL	RR 3.37 (2.464, 4.611)	A large reduction in Hb over time is an independent risk factor for all-cause mortality compared with no reduction in Hb P<0.001
All-cause mortality N=NR	Δ Hb > –3 to –2 g/dL	Δ Hb >0–1 g/dL	RR 1.466 (1.092, 1.969)	A moderate reduction in Hb over time is an independent risk factor for all-cause mortality compared with no reduction in Hb P=0.0109
All-cause mortality N=NR	Δ Hb > –2 to –1 g/dL	Δ Hb >0–1 g/dL	RR 1.178 (0.944, 1.471)	A small reduction in Hb over time is not an independent risk factor for all-cause mortality compared with no reduction in Hb P=0.1474
All-cause mortality N=NR	Δ Hb > –1 to 0 g/dL	Δ Hb >0–1 g/dL	RR 1.005 (0.831, 1.215)	A very small reduction in Hb over time is not an independent risk factor for all-cause mortality compared with no reduction in Hb P=0.9595
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with chronic heart failure.				
Applicability				
The study was conducted in a number of countries (Austria, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Norway, Portugal, Sweden, Switzerland, UK) so the results are likely to be applicable to the Australian setting.				

Comments
The authors conclude that “anaemia is common in patients with CHF and of independent prognostic value”. Other variables shown to be independent predictors of increased mortality were increasing age, NYHA class II and IV, increasing creatinine, diabetes, increasing duration of heart failure, ischaemic aetiology, and anticoagulant use.

ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomised controlled trial; RR, risk ratio; SBP, systolic blood pressure; UK, United Kingdom; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Maggioni et al (2005) Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. Journal of Cardiac Failure 11(2): 91–97.		
Affiliation/Source of funds		
Italian Association of Hospital Cardiologists Research Center, Florence, Italy; Salvatore Maugeri Foundation, Department of Cardiology, Pavia, Italy; University of Minnesota, Minneapolis, US; Mario Negri Institute, Milan, Italy; Ospedale Civile, Department of Cardiology, San Bonifacio, Italy; IRCCS S. Matteo Hospital, Department of Cardiology. Pavia, Italy. Funding of the Val-HeFT trial was provided by Novartis Pharma, Basel, Switzerland. The IN-CHF registry was partially supported by Merck Sharpe Dohme, Italy.		
Study design	Level of evidence	Location/setting
1. Re-analysis of double-blind RCT (Val-HeFT) 2. Prospective registry (IN-CHF)	Level II	1. Multicentre (US, Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, The Netherlands, Norway, South Africa, Spain, Sweden, UK). 2. Multicentre (Italy)
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (WHO)	Age, sex, SBP, heart rate, NYHA class, presence of coronary heart disease aetiology, ejection fraction, third heart sound, BMI, creatinine, use of ACEIs and β-blockers.	
Population characteristics (including size)		
1. Patients with heart failure: ≥ 18 years; history and clinical findings of heart failure for at least 3 months before screening; NYHA class II-IV; clinically stable; on a stable dose drug regimen that might include ACEI, diuretic, digoxin or β-blockers for at least 2 weeks; documented LVEF < 40% and echocardiographically measured left ventricular internal diameter in diastole/body surface area>2.9 cm/m^2. 2. Diagnosis of heart failure according to the criteria described by the European Society of Cardiology		
Length of follow-up	Outcomes measured	
1. 2 years 2. 1 year	All-cause mortality	
Method of analysis		
A Cox's proportional hazards model was applied to both the IN-CHF Registry and the Val-HeFT trial. For both analyses, the covariates described above were examined.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Data analysed from one prospective registry and one double-blind RCT; consecutive patients included in Registry (no further detail on patients agreeing to take part or loss to follow-up; all 5010 patients from RCT included in analysis; multivariate analysis conducted adjusting for a large number of potential confounding variables; follow-up for 1 and 2 years for RCT and 1 year for Registry.		
RESULTS		

Population	With risk factor	Without risk factor
IN-CHF	375	2036
Val-HeFT	453	4557

Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
2-year all-cause mortality (Val-HeFT) N=5010	Anaemia (WHO)	No anaemia	HR 1.26 (1.04, 1.52)	*Anaemia is an independent risk factor for all-cause mortality compared with no anaemia* P<0.05
1-year all-cause mortality (IN-CHF) N=2411	Anaemia (WHO)	No anaemia	HR 1.54 (1.20, 1.97)	*Anaemia is an independent risk factor for all-cause mortality compared with no anaemia* P<0.05
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value
2-year all-cause mortality (Val-He-FT) N=5010	1 g/dL increase in Hb		HR 0.922 (0.881, 0.966)	*A 1 g/dL increase in Hb is associated with a 7.8% reduction in mortality* P<0.05
1-year all-cause mortality (Val-He-FT) N=5010	1 g/dL increase in Hb		HR 0.89 (0.83, 0.95)	*A 1 g/dL increase in Hb is associated with an 11% reduction in mortality* P<0.05
1-year all-cause mortality (IN-CHF) N=2411	1 g/dL increase in Hb		HR 0.903 (0.839, 0.973)	*A 1 g/dL increase in Hb is associated with an 9.7% reduction in mortality* P<0.05
EXTERNAL VALIDITY				
Generalisability				
The results of the Val-HeFT and IN-CHF analyses are generalisable to a population with chronic heart failure who are generally looked after by cardiologists. As noted by the authors, this population is likely to largely exclude an older population who are often looked after by geriatricians, internal medicine physicians and general practitioners. The authors also note that the results of the IN-CHF registry analysis are generalisable to a wider population as there were no exclusion criteria for this population so it was wider than that included in the Val-HeFT trial.				
Applicability				
The IN-CHF Registry was conducted at multiple sites in Italy, while the Val-HeFT trial was conducted in 16 countries including the US, Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, The Netherlands, Norway, South Africa, Spain, Sweden and the UK.				
Comments				
The authors conclude that "anemia was confirmed to be an independent negative prognostic factor in patients with heart failure. The authors also note that in this study, no attempt was made to investigate the cause of anaemia or its time course; therefore, it could not be determined if chronic versus temporary anaemia have different prognostic significant.				

ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; NYHA, New York Heart Association; RCT, randomised controlled trial; SBP, systolic blood pressure; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Maraldi et al (2006) Anemia, physical disability and survival in older patients with heart failure. Journal of Cardiac Failure 12(7): 533–539.		
Affiliation/Source of funds		
University of Florida, Gainesville, Florida; University of Ferrara, Italy; Catholic University of Sacred Heart, Rome, Italy; Ortho Biotech Clinical Affairs, LLC, Bridgewater, New Jersey. Data analysis was supported by an educational grant from Ortho Biotech Clinical Affairs.		
Study design	Level of evidence	Location/setting
Prospective hospital cohort	Level II	Multicentre (Italy)

Risk factor/s assessed	Potential confounding variables measured
Anaemia (WHO)	Physical disability analysis: age, gender, smoking, cognitive status, Short Physical Performance Battery score, SBP, DBP, heart rate, BMI, serum albumin, cholesterol, serum sodium, creatinine clearance, NYHA class, coronary heart disease, diabetes, stroke, cancer, COPD, Cumulative Illness Rating Scale score, use of ACEIs. Mortality analysis: age, gender, cognitive status, Short Physical Performance Battery score, SBP, DBP, heart rate, BMI, serum albumin, cholesterol, serum sodium, creatinine clearance, NYHA class, Cumulative Illness Rating Scale score, use of ACEIs.

Population characteristics (including size)
Non-disabled, hospitalised with heart failure and aged ≥ 65 years: heart diagnosis carried out by means of the Clinical History Form, resulting in a summary score with a score of > 4 corresponding to a diagnosis of heart failure. N=567 Mean age 78; 47% female.

Length of follow-up	Outcomes measured
1 year	Functional status (self-report activities of daily living); all-cause mortality

Method of analysis
Multivariable Cox proportional-hazard regression analysis adjusted for variables outlined above. The final models only included those factors that significantly predicted the 2 outcomes or materially hanged the odds ratio or hazard ratio estimates for anaemia.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good (mortality)/fair (disability) Description: Prospective hospital cohort; no patients had disability at baseline as they were already excluded from the population; of 587 potentially included subjects, 10 excluded as they had dementia or severe cognitive impairment (excluded to avoid potential misclassification of self-report functional status), ten others excluded due to missing Hb concentration; results adjusted for a large number of potential confounders; 12 month follow-up with visits at , 6 and 12 months after hospital discharge.
RESULTS

Population	With risk factor	Without risk factor
Available	587	

Analysed	253		314	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Disability All patients N=567	Anaemia (WHO)	No anaemia	OR 2.17 (1.12, 4.24)	*Anaemia is an independent predictor of disability compared with no anaemia* P<0.05
Disability Female N=266	Anaemia (WHO)	No anaemia	OR 2.62 (1.06, 6.50)	*Anaemia is an independent predictor of disability compared with no anaemia in females* P<0.05
Disability Male N=301	Anaemia (WHO)	No anaemia	OR 1.58 (0.33, 7.60)	*Anaemia is not an independent predictor of disability compared with no anaemia in males* P<0.05
All-cause mortality All patients N=567	Anaemia (WHO)	No anaemia	OR 1.15 (0.69, 1.91)	*Anaemia is not an independent predictor of mortality compared with no anaemia* P<0.05
All-cause mortality Female N=266	Anaemia (WHO)	No anaemia	OR 2.33 (1.02, 5.30)	*Anaemia is an independent predictor of mortality compared with no anaemia in females* P<0.05
All-cause mortality Male N=301	Anaemia (WHO)	No anaemia	OR 0.65 (0.32, 1.35)	*Anaemia is not an independent predictor of mortality compared with no anaemia in males* P<0.05
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of patients hospitalised with heart failure who are discharged without disability.				
Applicability				
This study was conducted at a number of centres in Italy so may be applicable to the Australian setting.				
Comments				
The authors conclude that "anemia is a predictor of physical disability in older heart failure patients, and in women anemia is associated with increased mortality". The authors note that the small number of events in men may have affected the results, and that the use of the diagnostic tool may have resulted in misclassification. They also note that the study did not include an objective measure of cardiac function and indices of haemodilution and as such they cannot exclude that part of the poor prognosis associated with anaemia might be related to residual confounding due to baseline cardiac dysfunction or volume overload.				

ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure; WHO, World Health Organisation.

STUDY DETAILS: Cohort study			
Citation			
Poole-Wilson et al (2003) Mode of death in heart failure: findings from the ATLAS trial. Heart 89: 42–48.			
Affiliation/Source of funds			
Imperial College, London, UK; University of Texas, Galveston, US; Aarhus University Hospital, Aarhus, Denmark; University of Hull, Hull, UK; University of California, San Francisco, US; Karolinska Institute, Stockholm, Sweden. Supported by grants from AstraZeneca.			
Study design	Level of evidence	Location/setting	
Cohort analysis of a double-blind RCT (ATLAS)	Level II	Hospital + community/Various	
Risk factor/s assessed	Potential confounding variables measured		
Various including Hb (continuous)	Hb analysis adjusted for: lisinopril dose, age, sex, IHD, LVEF, NYHA class, SBP, DBP, heart rate, drugs at randomisation including antidiabetic, aspirin, β-blockers, long-acting nitrates, short-acting nitrates, previous ACEI, antiarrythmics, calcium channel blockers, anticoagulants/warfarin.		
Population characteristics (including size)			
Adults with mild, moderate or severe chronic heart failure (NYHA class II-IV); mean age 64 years, 79% male, 90% Caucasian, 77% moderate heart failure. N=3164			
Length of follow-up	Outcomes measured		
39–58 months (mean 46 months)	Mortality (all-cause, cardiovascular, CHF, sudden, out of hospital)		
Method of analysis			
Competing risks analysis was used in which other modes of death are censored when one mode of death is being examined. Used a Cox proportional hazards model. Multivariate analysis was used to adjust for prognostic factors, but within a category, factors were not adjusted due to potential correlation (eg, in Hb analysis, other lab values were not adjusted for).			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Good Description: Cohort analysis of a double-blind RCT (ATLAS); all randomised subjects included in the analysis; analysis adjusted for a large number of potential confounders; deaths during the trial were adjudicated by a two member endpoint committee; mean follow-up 46 months.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	3164		
Analysed	3164		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value

Mortality (N=3164)	Hb increase (g/dL)	HR 0.983	*A 1 g/dL increase in Hb is <u>not</u> independently associated with a decrease in risk of mortality* P ≥ 0.05
Cardiovascular mortality (N=3164)	Hb increase (g/dL)	HR 0.999	*A 1 g/dL increase in Hb is <u>not</u> independently associated with a decrease in risk of cardiovascular mortality* P ≥ 0.05
CHF mortality (N=3164)	Hb increase (g/dL)	HR 0.927	*A 1 g/dL increase in Hb is independently associated with a 7.3% decrease in risk of CHF mortality* P < 0.05
Sudden death (N=3164)	Hb increase (g/dL)	HR 1.036	*A 1 g/dL increase in Hb is <u>not</u> independently associated with a decrease in risk of sudden death* P ≥ 0.05
Out-of-hospital death (N=3164)	Hb increase (g/dL)	HR 0.983	*A 1 g/dL increase in Hb is <u>not</u> independently associated with a decrease in risk of out-of-hospital death* P ≥ 0.05
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to adults with mild-severe chronic heart failure.			
Applicability			
This study was conducted in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Hungary, Ireland, the Netherlands, Norway, Portugal, Slovak Republic, Spain, Switzerland, United Kingdom, United States. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors found a large number of factors were independently associated with mortality risk. Hb level was significantly associated only with CHF death. They note that while there is an overlap in prediction markers, in general death from progressive heart failure is associated with several markers of more severe left ventricular dysfunction and neurohormonal activation, as well as ischaemic heart disease, whereas sudden death is most closely related to markers of ischaemic heart disease.			

ACEI, angiotensin-converting enzyme inhibitor; CHF, congestive heart failure; CI, confidence interval; DBP, diastolic blood pressure; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; IHD, in hospital death; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomised controlled trial; SBP, systolic blood pressure; UK, United Kingdom; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Young et al (2008) Relation of low haemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF Registry). American Journal of Cardiology 101:223–230.		
Affiliation/Source of funds		
Cleveland Clinic Foundation, Cleveland; Ohio State University, Columbus; Duke University Medical Center, Durham; Campbell University School of Pharmacy, Research Triangle Park; Northwestern University, Chicago; University of California Medical Center, San Diego; Baylor University Medical Centre, Dallas; US. Funded by GlaxoSmithKline.		
Study design	Level of evidence	Location/setting
Prospective hospital-based registry	Level II	US/hospital

Risk factor/s assessed	Potential confounding variables measured
Haemoglobin (continuous)	In-hospital mortality: age, race, heart rate, SBP, DBP, sodium, creatinine, heart failure as primary reason for admission, prior CVA/TIA, hyperlipidaemia, liver disease, recent smoker, COPD, peripheral vascular disease, no prior heart failure, LVSD, ACEI, β-blocker. Post-discharge mortality: SBP, creatinine, age, reactive airway disease, weight, lower extremity oedema, statin at discharge, sodium, depression, β-blocker, discharge SBP, liver disease. (from www.optimize-hf.org)

Population characteristics (including size)
Patients hospitalised for an episode of a new or worsening heart failure as the primary cause of admission, or if significant HF symptoms developed for another primary diagnosis and HF was given as the primary discharge diagnosis; Full population N=48,612; subgroup population with follow-up N=5791; states that demographics and baseline demographics similar between 2 groups. Age 73.2 years; women 51.6%.

Length of follow-up	Outcomes measured
In-hospital or 60–90 days.	In-hospital mortality; 60–90 day mortality; 60–90 day mortality/rehospitalisation.

Method of analysis
A logistic multivariable model was used for in-hospital mortality and a Cox proportional hazards model was used for 60–90 day follow-up.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Fair Description: Prospective, hospital-based registry; > 48,000 included in registry while 10% (>5,000) were followed for 60–90 days – it is somewhat unclear whether the in-hospital mortality analysis includes the full cohort or subgroup; states that full cohort and subgroup were similar demographically; multivariate analysis includes a large number of potential confounders identified via univariate analysis or previous studies.
RESULTS

Population	With risk factor	Without risk factor
Available	48,612 (follow-up subgroup 5,791)	
Analysed	48,612 (follow-up subgroup 5,791)	

Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
In-hospital mortality (N=48,612)[a]	Hb decrease (up to 13 g/dL)	OR 1.077 (1.031, 1.126)	*A 1 g/dL decrease in Hb is associated with a 7.7% increase in the risk of in-hospital mortality* P=0.001
60–90-day mortality (N=5791)[a]	Hb decrease (up to 13 g/dL)	OR 1.021 (0.945, 1.104)	*A 1 g/dL decrease in Hb is not associated with a change in the risk of 60–90 day mortality* P=0.5939
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population admitted with a primary diagnosis of heart failure, or those admitted for another diagnosis where heart failure is the primary diagnosis at discharge.			
Applicability			
This study was conducted at multiple sites in the US. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors note that the study did not track changes in haemoglobin during hospitalisation, or whether treatment for anaemia was given. They also note that haemodilution may have contributed to the high prevalence of anaemia.			

ACEI, angiotensin-converting enzyme inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; DBP, diastolic blood pressure; dL, decilitre; g, grams; Hb, haemoglobin; HF, heart failure; LVSD, left ventricular systolic dysfunction; OR, odds ratio; SBP, systolic blood pressure; US, United States of America.

[a] Assumed to include the full cohort.

Elderly

Level II evidence

STUDY DETAILS: Cohort study		
Citation		
Chaves et al (2004) What constitutes normal haemoglobin concentration in community-dwelling disabled older women? J Am Geriatr Soc 52: 1811–1816.		
Affiliation/Source of funds		
John Hopkins University, Baltimore, US; Rio de Janeiro State University, Rio de Janeiro, Brazil; National Institute on Aging, Bethesda, US; University of Ferrara, Ferrara, Italy. Funded by the National Institute on Aging.		
Study design	Level of evidence	Location/setting
Prospective population-based cohort	Level II	US/community

Risk factor/s assessed	Potential confounding variables measured
Haemoglobin (various categories)	Age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV_1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.
Population characteristics (including size)	
Women aged ≥ 65 years, Medicare-eligible, a MMSE ≥ 18 and self-reported difficulty performing activities in two or more physical function domains; mean age 78.2 years, race 72% Caucasian.	
Length of follow-up	Outcomes measured
Median 5 years; maximum 6 years.	All-cause mortality
Method of analysis	
Cox-proportional hazards regression with adjustment for a wide range of potential confounders.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: Prospective, population-based cohort; 31.5% of eligible subjects did not agree to have blood sample taken (these subjects were older, had more disability and poorer cognitive function so results may underestimate association between Hb and mortality); mortality data obtained for all but 1.7% of subjects; large number of potential confounding variables included in analysis; follow-up median 5 years, maximum 6 years.	

RESULTS				
Population	With risk factor		Without risk factor	
Available	1002			
Analysed	686			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All-cause mortality (N=NR)[a]	Hb 8 g/dL	Hb 12 g/dL (low-normal)	HR 2.3 (1.3, 4.0)	*A Hb of 8 g/dL is an independent risk factor for increased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 8.5 g/dL	Hb 12 g/dL (low-normal)	HR 2.0 (1.2, 3.4)	*A Hb of 8.5 g/dL is an independent risk factor for increased all-cause mortality compared with a low-normal Hb* P=NR

All-cause mortality (N=NR)[a]	Hb 9 g/dL	Hb 12 g/dL (low-normal)	HR 1.8 (1.2, 2.8)	*A Hb of 9 g/dL is an independent risk factor for increased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 9.5 g/dL	Hb 12 g/dL (low-normal)	HR 1.7 (1.2, 2.4)	*A Hb of 9.5 g/dL is an independent risk factor for increased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 10 g/dL	Hb 12 g/dL (low-normal)	HR 1.5 (1.1, 2.0)	*A Hb of 10 g/dL is an independent risk factor for increased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 11 g/dL	Hb 12 g/dL (low-normal)	HR 1.2 (1.1, 1.4)	*A Hb of 11 g/dL is an independent risk factor for increased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 12.5 g/dL	Hb 12 g/dL (low-normal)	HR 0.90 (0.84, 0.97)	*A Hb of 12.5 g/dL is an independent risk factor for decreased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 13 g/dL	Hb 12 g/dL (low-normal)	HR 0.82 (0.71, 0.94)	*A Hb of 13 g/dL is an independent risk factor for decreased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 13.5 g/dL	Hb 12 g/dL (low-normal)	HR 0.76 (0.63, 0.92)	*A Hb of 13.5 g/dL is an independent risk factor for decreased all-cause mortality compared with a low-normal Hb* P=NR
All-cause mortality (N=NR)[a]	Hb 14 g/dL (mid-normal Hb)	Hb 12 g/dL (low-normal)	HR 0.74 (0.59, 0.92)	*A Hb of 14 g/dL is an independent risk factor for decreased all-cause mortality compared with a low-normal Hb* P=NR

All-cause mortality (N=NR)[a]	Hb 14.5 g/dL (mid-normal Hb)	Hb 12 g/dL (low-normal)	HR 0.75 (0.57, 0.98)	*A Hb of 14.5 g/dL is an independent risk factor for decreased all-cause mortality compared with a low-normal Hb* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of community-dwelling disabled women aged ≥ 65 years.				
Applicability				
This study was conducted in the US. The results are likely to be generalisable to the Australian setting.				
Comments				
The authors make a number of important observations about the results of their study. They state that they confirm previous findings that WHO-defined anaemia is an independent risk factor for mortality in older adults, but also that "Hb currently perceived as low-normal might independently contribute to increased mortality and that mid-normal Hb might be physiologically best". They also note the possibility of residual confounding from chronic disease burden, although they state they have made comprehensive (and perhaps, over adjustment). Finally, they note the large proportion of patients excluded from the analysis who did not want a blood sample taken. As these subjects were older and had more disease and disability, they state that their results may be an underestimate of the association between Hb and mortality risk. It should be noted that there were 686 subjects, separated into 16 Hb categories, with adjustment for a large number of potential confounding variables. This may have impacted on the results of the analysis.				

BMI, body mass index; CI, confidence interval; dL, decilitre; FEV_1, forced expiratory volume in 1 second; g, grams; Hb, haemoglobin; HR, hazard ratio; MMSE, mini-mental state examination; NR, not reported; TSH, thyroid stimulating hormone; US, United States of America; WHO, World Health Organisation.

[a] Total study includes 686 women.

STUDY DETAILS: Cohort study		
Citation		
Denny et al (2006) Impact of anemia on mortality, cognition, and function in community-dwelling elderly. American Journal of Medicine 119: 327–334.		
Affiliation/Source of funds		
Duke University, Durham, US; VA Medical Center, Durham, US. Funded by the National Institute on Aging and the John A Hartford Foundation Center of Excellence.		
Study design	Level of evidence	Location/setting
Prospective, population-based cohort	Level II	US/community
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (WHO and categorical)	Age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.	
Population characteristics (including size)		
Community-dwelling adults aged ≥ 65 years at enrolment; at the time of baseline Hb measurement (at visit 6) participants were aged ≥ 71 years; mean age 78 (range 71–102), female 65%, African-American 54%. N=1744		
Length of follow-up	Outcomes measured	

8 years	All-cause mortality; functional status; cognition.			
Method of analysis				
Cox-proportional hazards model was used to examine the adjusted risk-ratios for survival separately by anaemic status and by race, and overall.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective, population-based cohort; 1744 out of initial 2569 subjects had Hb levels measured, of those mortality status was obtained for 1701 after 8 years; analyses adjusted for a number of potential confounding variables; mortality determined by a search of the National Death Index; 8 years follow-up.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	426		1318	
Analysed	1701			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All-cause mortality (N=1701)	Anaemia (WHO)	No anaemia	RR 1.4 (1.2, 1.6)	*Anaemia is an independent risk factor for all-cause mortality compared with no anaemia* P=NR
All-cause mortality (N=1134) Women only	Anaemia (WHO)	No anaemia	RR 1.4 (1.2, 1.8)	*Anaemia is an independent risk factor in women for all-cause mortality compared with no anaemia* P=NR
All-cause mortality (N=567) Men only	Anaemia (WHO)	No anaemia	RR 1.3 (1.0, 1.7)	*Anaemia may be an independent risk factor in men for all-cause mortality compared with no anaemia* P=NR
All-cause mortality (N=765) Caucasian only	Anaemia (WHO)	No anaemia	RR 1.3 (1.0, 1.6)	*Anaemia may be an independent risk factor in a Caucasian population for all-cause mortality compared with no anaemia* P=NR

All-cause mortality (N=936) African-American only	Anaemia (WHO)	No anaemia	RR 1.4 (1.2, 1.8)	*Anaemia is an independent risk factor in an African-American population for all-cause mortality compared with no anaemia* P=NR
All-cause mortality (N=1134) Women only	Hb 0–10 g/dL	Hb 12–13 g/dL	RR 1.9 (1.2, 3.0)	*Hb 0–10 g/dL is an independent risk factor in women for all-cause mortality compared with Hb 12–13 g/dL* P=NR
All-cause mortality (N=1134) Women only	Hb 10–11 g/dL	Hb 12–13 g/dL	RR 2.2 (1.5, 3.1)[a]	*Hb 10–11 g/dL is an independent risk factor in women for all-cause mortality compared with Hb 12–13 g/dL* P=NR
All-cause mortality (N=1134) Women only	Hb 11–12 g/dL	Hb 12–13 g/dL	RR 1.2 (1.0, 1.8)	*Hb 11–12 g/dL may be an independent risk factor in women for all-cause mortality compared with Hb 12–13 g/dL* P=NR
All-cause mortality (N=567) Men only	Hb 0–10 g/dL	Hb 13–14 g/dL	RR 1.3 (0.5, 3.3)	*Hb 0–10 g/dL is not an independent risk factor in men for all-cause mortality compared with Hb 13–14 g/dL* P=NR
All-cause mortality (N=567) Men only	Hb 10–11 g/dL	Hb 13–14 g/dL	RR 1.7 (0.9, 3.3)	*Hb 10–11 g/dL is not an independent risk factor in men for all-cause mortality compared with Hb 13–14 g/dL* P=NR
All-cause mortality (N=567) Men only	Hb 11–12 g/dL	Hb 13–14 g/dL	RR 1.3 (0.7, 2.4)	*Hb 11–12 g/dL is not an independent risk factor in men for all-cause mortality compared with Hb 13–14 g/dL* P=NR
All-cause mortality (N=567) Men only	Hb 12–13 g/dL	Hb 13–14 g/dL	RR 1.2 (0.9, 1.7)	*Hb 12–13 g/dL is not an independent risk factor in men for all-cause mortality compared with Hb 13–14 g/dL* P=NR

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to a community-dwelling population aged at least 71 years.
Applicability
This study was conducted in the US and an African-American population was oversampled and made up > 50% of the population. The results of this study may be applicable to the Australian setting.
Comments
The authors note that this is the first study to examine whether racial differences in the prevalence of anaemia translate to increased mortality. The results showed that African-Americans with anaemia did not have a significantly higher mortality rate compared with Caucasians with anaemia after adjusting for differences in health condition and chronic disease burden. They note limits of their study including the possibility of unidentified confounding, potential bias due to patient self-report of clinical disease and lack of information of cause of anaemia or possible treatment for anaemia. They also note that patients not included in the analysis were generally older and more impaired and so the risk associated with anemia may be underestimated.

BMI, body mass index; CI, confidence interval; dL, decilitre; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

[a] Different RRs shown in the table (2.2) and text (2.1) of this publication. The table RR has been used here.

STUDY DETAILS: Cohort study		
Citation		
Dong et al (2008) A population-based study of hemoglobin, race and mortality in elderly persons. Journal of Gerontology 63A(8): 873–878.		
Affiliation/Source of funds		
Rush University medical Center, Chicago, US; University of Chicago, Chicago, US; PATH Inc, Seattle, US. Supported by a National Institute on Aging grant.		
Study design	Level of evidence	Location/setting
Prospective, community-based cohort study	Level II	Community/US
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (WHO)	Age, sex, education, race, global cognition, income, coronary artery disease, diabetes, hypertension, stroke, cancer, hip fracture, Katz ADL, Center for Epidemiological Study of Depression scale, smoking status, self-reported health status, BMI, GFR, serum cholesterol, mean cell volume.	
Population characteristics (including size)		
Randomly selected residents aged ≥ 65 years residing in three adjacent neighbourhoods in Chicago; mean age 80 years, 58.4% female, 49.7% Black.		
Length of follow-up	Outcomes measured	
Mean 3.9 years (median 3.5 years)	Mortality	
Method of analysis		
Cox proportional hazards model used to test the association between baseline Hb and mortality.		

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective, community-based cohort study; residents turning 65 randomly selected at each 3-year study cycle for inclusion; no discussion of subjects who refused to participate; analyses adjusted for a large number of potential confounding factors; outcome measured via informants, newspaper obituaries and verified through matching with the National death Index; mean 3.9 year follow-up.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	508		1298	
Analysed	508		1298	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (N=897) Black	Anaemia (WHO)	No anaemia	HR 1.90 (1.43, 2.53)	*Anaemia is an independent risk factor for increased mortality* P=NR
Mortality (N=909) White	Anaemia (WHO)	No anaemia	HR 1.85 (1.32, 2.59)	*Anaemia is an independent risk factor for increased mortality* P=NR
Mortality (N=NR) Black	Hb > 1 g/dL below WHO	Hb 1.1–2 g/dL above WHO	HR 1.95 (1.24, 3.06)	*Hb > 1 g/dL below the WHO cut-off is an independent risk factor for increased mortality compared with Hb 1.1–2 g/dL above the WHO cut-off* P=NR
Mortality (N=NR) White	Hb > 1 g/dL below WHO	Hb 1.1–2 g/dL above WHO	HR 2.17 (1.28, 3.65)	*Hb > 1 g/dL below the WHO cut-off is an independent risk factor for increased mortality compared with Hb 1.1–2 g/dL above the WHO cut-off* P=NR
Mortality (N=NR) Black	Hb 0–0.9 g/dL below WHO	Hb 1.1–2 g/dL above WHO	HR 1.35 (0.88, 2.05)	*Hb 0–0.9 g/dL below the WHO cut-off is not an independent risk factor for increased mortality compared with Hb 1.1–2 g/dL above the WHO cut-off* P=NR

Mortality (N=NR) White	Hb 0–0.9 g/dL below WHO	Hb 1.1–2 g/dL above WHO	HR 2.14 (1.39, 3.30)	*Hb 0–0.9 g/dL below the WHO cut-off is an independent risk factor for increased mortality compared with Hb 1.1–2 g/dL above the WHO cut-off* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of community-dwelling adults aged ≥ 65 years, regardless of functional status.				
Applicability				
This study was conducted in a specific region of the US, south side Chicago, which the authors state includes a reasonable distribution of socioeconomic characteristics within each racial/ethnic group. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that "both anemia by WHO criteria and mild reductions in Hb were related to increased risk of mortality in older blacks and whites". The authors also note that "the statistical interaction between race and anemia was not statistically significant, suggesting that the increased mortality of anemia did not differ strongly by race". The authors note a number of limitations of the study including: (i) the possibility of residual confounding; (ii) the lack of data on the aetiology of anaemia; and (iii) the lack of data on change in Hb over time.				

ADL, activities of daily living; BMI, body mass index; CI, confidence interval; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; NR, not reported; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Endres et al (2009) Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. Current Medical Research and Opinion 25(5): 1143–1158.		
Affiliation/Source of funds		
Ruhr University Bochum, Bochum, Germany; Friedrich Schiller University Jena, Germany; Technical University of Dresden, Dresden, Germany; Ruhr, University Bochum, Herne, Germany; University of Heidelberg, Karlsbad-Langensteinbach, Germany. Funded by an unrestricted educational grant from Sanofi-Aventis, berline and a grant from the German Federal Ministry of Education and Research (BMBF).		
Study design	Level of evidence	Location/setting
Prospective, primary care-based cohort	Level II	Germany/primary-care
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (WHO). It should be noted that there were very few subjects with Hb < 10 g/dL so the authors have labelled the population as mildly anaemic.	Age, BMI, diabetes, TC/HDL, MI, stroke, PAD, smoking, HCY, hs-CRP, eCRP, eGFR, high-school graduation.	
Population characteristics (including size)		

Community-dwelling, primary-care patients aged ≥ 65 years, able to co-operate and provide written informed consent and a life expectancy > 6 months as judged by the treating family physician; mean age 72.5 years; female 57.8%. N=6880				
Length of follow-up	Outcomes measured			
Maximum 5.3 years	All-cause mortality, non-cancer mortality			
Method of analysis				
Used a Cox proportional hazards model to evaluate the association between presence of anaemia and death from any cause. Two models were used: (i) adjusted for age only (not shown here) and (ii) adjusted for a number of clinically meaningful variables and variable which had a p value of < 0.2 after backward selection.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Prospective, primary care-based cohort; 344 family physicians recruited 6880 patients, only 4 lost to follow-up; analyses adjusted for a large number of potential confounding factors; mortality collected by case-report forms submitted by clinicians or by consulting records kept by residency registration offices; maximum 5.3 years follow-up.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	472		6408	
Analysed	6876			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All-cause mortality (N=3975) Women only	Anaemia (WHO)	No anaemia	HR 1.13 (0.79, 1.61)	*Anaemia is not an independent risk factor in women for all-cause mortality* P= 0.51
All-cause mortality (N=2901) Men only	Anaemia (WHO)	No anaemia	HR 1.89 (1.47, 2.44)	*Anaemia is an independent risk factor in men for all-cause mortality* P= <0.001
Non-cancer mortality (N=3865) Women only	Anaemia (WHO)	No anaemia	HR 1.20 (0.81, 1.79)	*Anaemia is not an independent risk factor in women for non-cancer mortality* P= 0.360
Non-cancer mortality (N=2760) Men only	Anaemia (WHO)	No anaemia	HR 1.66 (1.21, 2.27)	*Anaemia is an independent risk factor in men for non-cancer mortality* P= 0.002
EXTERNAL VALIDITY				
Generalisability				

The results of this study are generalisable to a mildly anaemic, community-dwelling population aged ≥ 65 years without significant co-morbidity.
Applicability
This study was conducted in Germany. The results of this study are likely to be applicable to the Australian setting.
Comments
The authors note that even mild anaemia is an independent risk factor for mortality (both all-cause and non-cancer) in elderly, apparently healthy men but not women. They note that Hb levels < 10 g/dL were almost non-existent in their population, which is in keeping with the absence of severe co-morbidities. They suggest that the marked gender difference in results may be related to differences in the prevalence and incidence of obstructive sleep apnoea, which wasn't measured in their cohort. They note that a strength of their study is the large sample size, the choice of population, the monitoring of all centres and excellent follow-up (>99.9% reporting of survival status).They note limitations as the solely Caucasian population which may limit generalisability.

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; dL, decilitre; eCRP, estimated C-reactive protein; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HCY, homocysteine; HR, hazard ratio; MI, myocardial infarction; NR, not reported; PAD, peripheral artery disease; TC/HDL, total cholesterol/high-density lipoprotein cholesterol ratio; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Izaks et al (1999) The definition of anemia in older persons. JAMA 281(18): 1714–1717.		
Affiliation/Source of funds		
Leiden University Medical Center, Leiden, the Netherlands. This study was supported by grants from the National Institutes of Health, Bethesda, US and the Office for Old Age Affairs of the Dutch Ministry of Public Health, Welfare and Sports, The Hague, the Netherlands.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	The Netherlands/community
Risk factor/s assessed	Potential confounding variables measured	
Anaemia (WHO)	1. Age and sex; (2) age, sex and self-reported diseases at baseline associated with anaemia including malignant neoplasm, infectious disease, thyroid disease, peptic ulcer, renal failure, and rheumatoid disease; (3) age, sex and functional status defined as any dependency in activities of daily living and cognitive impairment as measured by a MMSE < 24 points; (4) age and sex and only in those without self-reported disease.	
Population characteristics (including size)		
Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study; 73% women, median age 89. N=755.		
Length of follow-up	Outcomes measured	
10 years	10-year survival	
Method of analysis		
Mortality risk was estimated by a Cox proportional-hazards regression model adjusted for the above-mentioned potential confounders.		

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective, community-based cohort study; 75% of the eligible population included in the analysis; the analysis adjusted for a number of factors, but these are done in separate analyses; mortality data was gathered from death certificates obtained from the civic registries; follow-up was 10 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	1016			
Analysed	151		604	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
0–5 year mortality (N=755) Age and sex adjusted	Anaemia (WHO)	No anaemia	1.84 (1.50, 2.25)	*Anaemia is an independent risk factor for 0–5 year mortality* P=NR
0–5 year mortality (N= 544) Age adjusted/women only	Anaemia (WHO)(n=91)	No anaemia(n=453)	1.60 (1.24, 2.06)	*Anaemia is an independent risk factor for 0–5 year mortality in women* P <0.001
0–5 year mortality (N= 211) Age adjusted/men only	Anaemia (WHO)(n=60)	No anaemia(n=151)	2.29 (1.60, 3.26)	*Anaemia is an independent risk factor for 0–5 year mortality in men* P=<0.001
0–5 year mortality (N= 617) Age and sex adjusted	Microcytic anaemia (WHO) (n=13)	No anaemia(n = 604)	1.84 (1.01, 3.35)	*Microcytic anaemia is an independent risk factor for 0–5 year mortality* P=NR
0–5 year mortality (N=732) Age and sex adjusted	Normocytic anaemia[a] (WHO)	No anaemia	1.86 (1.51, 2.31)	*Normocytic anaemia is an independent risk factor for 0–5 year mortality* P=NR
0–5 year mortality (N=614) Age and sex adjusted	Macrocytic anaemia (WHO)	No anaemia	1.52 (0.78, 2.96)	*Macrocytic anaemia is not an independent risk factor for 0–5 year mortality* P=NR
0–5 year mortality (N=755) Age, sex and disease adjusted	Anaemia (WHO)	No anaemia	1.84 (1.49, 2.27)	*Anaemia is an independent risk factor for 0–5 year mortality* P=NR

0–5 year mortality (N=755) Age, sex and functional status adjusted	Anaemia (WHO)	No anaemia	1.74 (1.41, 2.15)	*Anaemia is an independent risk factor for 0–5 year mortality* P=NR
0–5 year mortality (N=755) Age and sex and excludes patients with clinical disease	Anaemia (WHO)	No anaemia	2.21 (1.37, 3.57)	*Anaemia is an independent risk factor for 0–5 year mortality* P=NR
5–10 year mortality (N=755) Age and sex adjusted	Anaemia (WHO)	No anaemia	0.99 (0.56, 1.76)	*Anaemia is not an independent risk factor for 5–10 year mortality* P=NR
5–10 year mortality (N= 617) Age and sex adjusted	Microcytic anaemia (WHO)	No anaemia	-	-
5–10 year mortality (N=732) Age and sex adjusted	Normocytic anaemia[a] (WHO)	No anaemia	0.90 (0.52, 1.79)	*Anaemia is not an independent risk factor for 5–10 year mortality* P=NR
5–10 year mortality (N=614) Age and sex adjusted	Macrocytic anaemia (WHO)	No anaemia	-	-
5–10 year mortality (N=755) Age, sex and disease adjusted	Anaemia (WHO)	No anaemia	0.91 (0.50, 1.64)	*Anaemia is not an independent risk factor for 5–10 year mortality* P=NR
5–10 year mortality (N=755) Age, sex and functional status adjusted	Anaemia (WHO)	No anaemia	1.07 (0.74, 2.33)	*Anaemia is not an independent risk factor for 5–10 year mortality* P=NR
5–10 year mortality (N=755) Age and sex and excludes patients with clinical disease	Anaemia (WHO)	No anaemia	0.64 (0.15, 2.68)	*Anaemia is not an independent risk factor for 5–10 year mortality* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a community-based population aged ≥ 85 years.				
Applicability				
This study was conducted in the Netherlands. The results of this study are likely to be applicable to the Australian setting.				

Comments
The authors conclude that "anemia defined by the WHO criteria was associated with an increased mortality risk in persons aged 85 years and older". The authors note that the association between low haemoglobin and mortality could not be explained by diseases at baseline or functional impairment, and low haemoglobin was associated with increased mortality risk even in subjects without clinical disease. They also state that the evidence suggests that the higher frequency of anaemia in men can be explained by a higher prevalence of underlying diseases.

CI, confidence interval; MMSE, mini-mental state examination; NR, not reported; WHO, World Health Organisation.

[a] Defined as 80–100 mg/dL.

STUDY DETAILS: Cohort study		
Citation		
Lucca et al (2008) Association of mild anemia with cognitive, functional, mood and quality of life outcomes in the elderly: the "Health and Anemia" study. PLoS ONE 3(4): e1920. Doi: 10.1371/journal.pone.0001920.		
Affiliation/Source of funds		
Instituto di Ricerche Farmacologiche "Mario Negri", Milano; Ospedale degli Infermi, Biella; Local Health Authority, ASL12, Biella; Italy		
Study design	Level of evidence	Location/setting
Cross-sectional cohort study	Level II	Community/Italy
Risk factor/s assessed	Potential confounding variables measured	
Mild anaemia (WHO definition or higher, modified definition)	Cancer status, age, sex, education, depressive symptoms, hypertension, heart failure, myocardial infarction, diabetes, respiratory failure and neurologic diseases.	
Population characteristics (including size)		
Residents of Biella, Italy, aged 65–84 without neurological or psychiatric disease, severe sensory deficits, renal insufficiency, severe organ insufficiency, terminal illness, hospitalisation, institutionalisation and illiteracy; mean age ~73 years, female ~ 53%.		
Length of follow-up	Outcomes measured	
Cross-sectional (QoL data collected a mean of 46 days after Hb measurement)	Functional/performance status (SF-12, FACT-An, IADL)	
Method of analysis		
Used multivariable analysis to assess independent association between mild anaemia and QoL		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Prospective cross-sectional study; of 10,110 potentially eligible residents, 4501 agreed to take part and accepted the blood tests and health questionnaire (those who refused were slightly older [1 year]; of those, 4068 were then considered eligible (265 anaemia and 4157 anaemia); 170/265 anaemia residents had mild anaemia and completed the blood tests and interview while 547/4068 non-anaemia residents were randomised and completed the blood tests and interview; residents included and excluded were compared and the only differences were less women taking part (8.7%), more with a history of MI (1.8%) and more educated (0.5 years); the two latter variable are thought to be associated with the difference in women; the analysis was adjusted for a large number of potential confounding and a number of sensitivity analyses were undertaken including for disease severity, cancer and renal disease; interviews conducted by nurses and psychologists with high agreement between them (Cohen's κ 0.84–0.93).		

RESULTS				
Population	With risk factor		Without risk factor	
Available	249		3803	
Analysed	170		547	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
SF-12 – Physical (0–100) (N=717)	Mild anaemia (WHO)[a]	No anaemia	45.3 ± 10.0 vs 47.3 ± 8.7	*Mild anaemia is not an independent risk factor for a lower mean SF-12-Physical score compared with no anaemia* P=0.1650
SF-12 – Physical (score < 40) (N=717)	Mild anaemia (WHO)[a]	No anaemia	29.9% vs 19.5%	*Mild anaemia is not an independent risk factor for SF-12-Physical score < 40 compared with no anaemia* P=0.0665
SF-12 – Mental (0–100) (N=717)	Mild anaemia (WHO)[a]	No anaemia	52.5 ± 8.6 vs 51.8 ± 9.1	*Mild anaemia is not an independent risk factor for a lower mean SF-12-Mental score compared with no anaemia* P=0.0991
SF-12 – Mental (score < 40) (N=717)	Mild anaemia (WHO)[a]	No anaemia	9.2% vs 11.3%	*Mild anaemia is not an independent risk factor for SF-12-Mental score < 40 compared with no anaemia* P=0.1323
FACT-An (0–188) (N=717)	Mild anaemia (WHO)[a]	No anaemia	136.7 ± 21.5 vs 141.0 ± 18.3	*Mild anaemia is not an independent risk factor for a lower mean FACT-An score compared with no anaemia* P=0.1770
FACT-General (0–108) (N=717)	Mild anaemia (WHO)[a]	No anaemia	73.8 ± 12.9 vs 75.8 ± 12.2	*Mild anaemia is not an independent risk factor for a lower mean FACT-General score compared with no anaemia* P=0.4003
FACT-An anaemia (0–80) (N=717)	Mild anaemia (WHO)[a]	No anaemia	62.7 ± 10.2 vs 65.1 ± 7.8	*Mild anaemia is an independent risk factor for a lower mean FACT-An anaemia score compared with no anaemia* P=0.0456

FACT-An fatigue (0–52) (N=717)	Mild anaemia (WHO)[a]	No anaemia	41.5 ± 7.7 vs 43.4 ± 5.8	*Mild anaemia is an independent risk factor for a lower mean FACT-An fatigue score compared with no anaemia* P=0.0109
IADL (% with disability > 5%) (N=717)	Mild anaemia (WHO)[a]	No anaemia	20.1% vs 11.2%	*Mild anaemia is not an independent risk factor for disability > 5% measured by the IADL* *P=0.1966*
SF-12 – Physical (0–100) (N=717)	Mild anaemia (modified)[b]	No anaemia	44.9 ± 10.1 vs 47.6 ± 8.5	*Mild anaemia is an independent risk factor for a lower mean SF-12-Physical score compared with no anaemia* P=0.0295
SF-12 – Physical (score < 40) (N=717)	Mild anaemia (modified)[b]	No anaemia	31.7% vs 18.6%	*Mild anaemia is an independent risk factor for SF-12-Physical score < 40 compared with no anaemia* P=0.0128
SF-12 – Mental (0–100) (N=717)	Mild anaemia (modified)[b]	No anaemia	52.2 ± 9.7 vs 51.9 ± 9.0	*Mild anaemia is not an independent risk factor for a lower mean SF-12-Mental score compared with no anaemia* P=0.1847
SF-12 – Mental (score < 40) (N=717)	Mild anaemia (modified)[b]	No anaemia	10.0% vs 11.3%	*Mild anaemia is not an independent risk factor for SF-12-Mental score < 40 compared with no anaemia* P=0.1323
FACT-An (0–188) (N=717)	Mild anaemia (modified)[b]	No anaemia	136.3 ± 21.6 vs 141.2 ± 21.6	*Mild anaemia is not an independent risk factor for a lower mean FACT-An score compared with no anaemia* P=0.0830
FACT-General (0–108) (N=717)	Mild anaemia (modified)[b]	No anaemia	73.7 ± 13.0 vs 75.9 ± 12.1	*Mild anaemia is not an independent risk factor for a lower mean FACT-General score compared with no anaemia* P=0.2942

FACT-An anaemia (0–80) (N=717)	Mild anaemia (modified)[b]	No anaemia	62.5 ± 10.3 vs 65.3 ± 7.6	*Mild anaemia is an independent risk factor for a lower mean FACT-An anaemia score compared with no anaemia* P=0.0099
FACT-An fatigue (0–52) (N=717)	Mild anaemia (modified)[b]	No anaemia	41.4 ± 7.8 vs 43.5 ± 5.6	*Mild anaemia is an independent risk factor for a lower mean FACT-An fatigue score compared with no anaemia* P=0.0032
IADL (% with disability > 5%) (N=717)	Mild anaemia (modified)[b]	No anaemia	20.0% vs 10.9%	*Mild anaemia is <u>not</u> an independent risk factor for disability > 5% measured by the IADL* *P=0.2042*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of community-dwelling elderly people aged 65–84.				
Applicability				
This study was conducted in a single town in Italy. The results of this study may be applicable to the Australian setting.				
Comments				
The authors conclude that the results "suggest an independent association of mild grade anemia with worse selective attention performance and disease-specific QoL ratings in the elderly persons living in the community". They note a number of limitations including: (i) use of self report (although they note the reliability of the interview was very high); (ii) non-response bias (although state that Hb status was unknown to participants); (iii) possibility of residual confounding (although state that large number of variables adjusted for may have led to underestimation of strength of association); and (iv) inability to determine causality.				

An, anaemia; CI, confidence interval; dL, decilitre; FACT; Functional Assessment of Cancer Therapy; g, grams ; IADL, Instrumental Activities of Daily Living; MI, myocardial infarction; QoL, quality of life; SF-12, Short Form (12) Health Survey; WHO, World Health Organisation.

[a] Defined as a Hb of 10–11.9 g/dL for women and 10–12.9 g/dL for men.

[b] Defined as a Hb of 10–12.1 g/dL for women and 10–13.1 g/dL for men.

STUDY DETAILS: Cohort study		
Citation		
Patel et al (2007) Racial variation in the relationship of anemia with mortality and mobility disability among older adults. Blood 109: 4663–4670.		
Affiliation/Source of funds		
National Institute on Aging, Bethesda, US; University of Tennessee, Memphis, US; University of California, San Francisco, US; University of Pittsburgh, Pittsburgh, US. Supported in part by National Institutes of Health, National Institute on Aging.		
Study design	Level of evidence	Location/setting
Prospective, community-based cohort	Level II	Community/US

Risk factor/s assessed	Potential confounding variables measured
Anaemia (WHO) and Hb level	Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.
Population characteristics (including size)	
Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71–82 without substantial disability; age ~ 75 years, male 48.2%. N=2601	
Length of follow-up	Outcomes measured
Up to 6 years	Mortality, mobility disability
Method of analysis	
Cox proportional hazards models were used to assess associations of WHO anaemia status and Hb levels with mortality and incidence of mobility disability.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: Prospective, community-based cohort study; 3075 initially recruited, Hb assessment occurred at the second year of follow-up and included 2601 participants; those not included were older, more likely to self-identify as black and had more medical conditions (ie, may have been at greater risk of mortality); only 2574 included in analysis – no details regarding this are provided; analysis adjusted for a large number of potential confounding factors; mortality assessed every six months by telephone contact and confirmed with death certificate; mobility difficulty defined as two consecutive reports of having a lot of difficulty or not being able to walk a quarter mile or up 10 steps without resting; follow-up up to 6 years.	
RESULTS	

Population	With risk factor		Without risk factor	
Available	399		2202	
Analysed	394		2180	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (N=1018) Blacks	Anaemia (WHO)	No anaemia	HR 1.28 (0.95, 1.70)	*Anaemia is not an independent risk factor for mortality in blacks* P=NR
Age and sex adjusted only				
Mortality (N=1583) Whites	Anaemia (WHO)	No anaemia	HR 2.19 (1.62, 2.95)	*Anaemia is an independent risk factor for mortality in whites* P=NR
Age and sex adjusted only				

Mortality (N=395) Blacks without major diseases	Anaemia (WHO)	No anaemia	HR 0.87 (0.43, 1.77)	*Anaemia is not an independent risk factor for mortality in blacks without major diseases* P=NR
Age and sex adjusted only				
Mortality (N=537) Whites without major diseases	Anaemia (WHO)	No anaemia	HR 2.07 (1.01, 4.22)	*Anaemia is an independent risk factor for mortality in whites without major diseases* P=NR
Age and sex adjusted only				
Mortality (N=587) Black women	Anaemia (WHO)	No anaemia	HR 1.17 (0.72, 1.89)	*Anaemia is not an independent risk factor for mortality in black women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=745) White women	Anaemia (WHO)	No anaemia	HR 2.68 (1.52, 4.69)	*Anaemia is an independent risk factor for mortality in white women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=416) Black men	Anaemia (WHO)	No anaemia	HR 0.88 (0.56, 1.38)	*Anaemia is not an independent risk factor for mortality in black men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=826) White men	Anaemia (WHO)	No anaemia	HR 1.62 (1.08, 2.44)	*Anaemia is an independent risk factor for mortality in white men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				

Mortality (N=234) Black women	Hb < 11.0 g/dL	Hb 12.0–12.9 g/dL	HR 0.77 (0.26, 2.25)	*Hb < 11.0 g/dL is not an independent risk factor for mortality compared with Hb 12.0–12.9 g/dL in black women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=300) Black women	Hb 11.0–11.9 g/dL	Hb 12.0–12.9 g/dL	HR 1.66 (0.92, 3.00)	*Hb 11.0–11.9 g/dL is not an independent risk factor for mortality compared with Hb 12.0–12.9 g/dL in black women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=185) White women	Hb < 11.0 g/dL	Hb 12.0–12.9 g/dL	HR 3.70 (1.55, 8.85)	*Hb < 11.0 g/dL is an independent risk factor for mortality compared with Hb 12.0–12.9 g/dL in white women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=206) White women	Hb 11.0–11.9 g/dL	Hb 12.0–12.9 g/dL	HR 2.90 (1.22, 6.90)	*Hb 11.0–11.9 g/dL is an independent risk factor for mortality compared with Hb 12.0–12.9 g/dL in white women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=162) Black men	Hb < 11.0 g/dL	Hb 13.0–13.9 g/dL	HR 1.74 (0.85, 3.57)	*Hb < 11.0 g/dL is not an independent risk factor for mortality compared with Hb 13.0–13.9 g/dL in black men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				

Mortality (N=166) Black men	Hb 11.0–11.9 g/dL	Hb 13.0–13.9 g/dL	HR 0.43 (0.17, 1.08)	*Hb 11.0–11.9 g/dL is not an independent risk factor for mortality compared with Hb 13.0–13.9 g/dL in black men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=206) Black men	Hb 12.0–12.9 g/dL	Hb 13.0–13.9 g/dL	HR 0.67 (0.37, 1.21)	*Hb 12.0–12.9 g/dL is not an independent risk factor for mortality compared with Hb 13.0–13.9 g/dL in black men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=182) White men	Hb < 11.0 g/dL	Hb 13.0–13.9 g/dL	HR 3.19 (1.04, 9.84)	*Hb < 11.0 g/dL is an independent risk factor for mortality compared with Hb 13.0–13.9 g/dL in white men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=197) White men	Hb 11.0–11.9 g/dL	Hb 13.0–13.9 g/dL	HR 2.23 (1.04, 4.76)	*Hb 11.0–11.9 g/dL is an independent risk factor for mortality compared with Hb 13.0–13.9 g/dL in white men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mortality (N=197) White men	Hb 12.0–12.9 g/dL	Hb 13.0–13.9 g/dL	HR 1.20 (0.69, 2.08)	*Hb 12.0–12.9 g/dL is not an independent risk factor for mortality compared with Hb 13.0–13.9 g/dL in white men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				

Mobility disability (N=497) Black women	Anaemia (WHO)	No anaemia	HR 1.00 (0.58, 1.72)	*Anaemia is not an independent risk factor for mobility disability in black women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mobility disability (N=685) White women	Anaemia (WHO)	No anaemia	HR 2.15 (1.05, 4.40)	*Anaemia is an independent risk factor for mobility disability in white women* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mobility disability (N=376) Black men	Anaemia (WHO)	No anaemia	HR 0.91 (0.45, 1.83)	*Anaemia is not an independent risk factor for mobility disability in back men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
Mobility disability (N=790) White men	Anaemia (WHO)	No anaemia	HR 1.60 (0.92, 2.78)	*Anaemia is not an independent risk factor for mobility disability in white men* P=NR
Adjusted for: Age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.				
EXTERNAL VALIDITY				
Generalisability				
This study is generalisable to a wide population of elderly subjects aged 71–82 years who were well functioning and who may or may not have had co-morbidities.				
Applicability				
This study was conducted in Memphis and Pittsburgh. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that "WHO-defined anaemia was significantly associated with an increased risk of mortality and mobility disability in whites, but not blacks". They also state that this is the first study to provide initial evidence that the haemoglobin "set-point" is lower in blacks than in whites. The authors also note that the participants in their study were healthier than those in other similar cohort studies. They note two limitations of their study including the timing of assessments (Hb measured at 2 years and cystatin C measured at baseline) and the generalisability of their cohort who were generally well functioning.				

BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study				
Citation				
Patel et al (2009) Haemoglobin concentration and the risk of death in older adults: differences by race/ethnicity in the NHANES III follow-up. British Journal of Haematology 145: 514–523.				
Affiliation/Source of funds				
National Institute on Aging, Bethesda, US; Johns Hopkins University School of Medicine, Baltimore, US. Supported by the Intramural Research program of the US National Institute on Aging, National Institutes of Health				
Study design	Level of evidence		Location/setting	
Prospective, population-based cohort	Level II		US/community	
Risk factor/s assessed		Potential confounding variables measured		
Anaemia (WHO) and Hb at various levels above or below WHO criteria		Age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.		
Population characteristics (including size)				
Civilian, non-institutionalised population aged ≥ 65 years who identified their race as non-Hispanic white, non-Hispanic black or Mexican American; mean age ~73 years; female ~57%. N=4089				
Length of follow-up		Outcomes measured		
12 years		All-cause mortality		
Method of analysis				
A Cox-proportional hazards model was used to assess the association of haemoglobin level with mortality, adjusting for all potential confounding factors.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Prospective, population-based cohort; of 5252 potentially eligible subjects, 4199 had haemoglobin values available for analysis and of those 4090 identified as one of the three racial groups under consideration; in one additional patient vital status could not be determined; therefore there were 4089 subjects available for analysis; the authors note that those with missing haemoglobin values were older, more likely to be female, and less likely to be Mexican-American than non-Hispanic white and more likely to die during follow-up; analyses adjusted for a large number of potential confounders; follow-up 12 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	5252			
Analysed	4089			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Non-Hispanic white				

12-year all-cause mortality (N=1018)	Hb > 1 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 2.11 (1.51, 2.94)	*A Hb level > 1 g/dL below the WHO cut-off is significantly associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=994)	Hb 0.51–1 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 2.04 (1.47, 2.84)	*A Hb level 0.51–1 g/dL below the WHO cut-off is significantly associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=1040)	Hb 0.01–0.5 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 1.43 (1.07, 1.92)	*A Hb level 0.01–0.5 g/dL below the WHO cut-off is significantly associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=1481)	Hb 0–0.99 g/dL above the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 1.24 (1.03, 1.51)	*A Hb level 0–0.99 g/dL above the WHO cut-off is significantly associated with an increased risk of mortality* P=NR
Non-Hispanic black				
12-year all-cause mortality (N=274)	Hb > 1 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 2.07 (1.26, 3.39)	*A Hb level > 1 g/dL below the WHO cut-off is significantly associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=237)	Hb 0.51–1 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 1.33 (0.82, 2.18)	*A Hb level 0.51–1 g/dL below the WHO cut-off is not associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=265)	Hb 0.01–0.5 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 0.73 (0.45, 1.19)	*A Hb level 0.01–0.5 g/dL below the WHO cut-off is not associated with an increased risk of mortality* P=NR

12-year all-cause mortality (N=427)	Hb 0–0.99 g/dL above the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 0.80 (0.57, 1.12)	*A Hb level 0–0.99 g/dL above the WHO cut-off is not associated with an increased risk of mortality* P=NR
Mexican American				
12-year all-cause mortality (N=242)	Hb > 1 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 4.56 (2.23, 9.31)	*A Hb level > 1 g/dL below the WHO cut-off is significantly associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=232)	Hb 0.51–1 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 1.47 (0.59, 3.65)	*A Hb level 0.51–1 g/dL below the WHO cut-off is not associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=246)	Hb 0.01–0.5 g/dL below the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 1.38 (0.73, 2.62)	*A Hb level 0.01–0.5 g/dL below the WHO cut-off is not associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=347)	Hb 0–0.99 g/dL above the WHO cut-off	1.0–1.99 g/dL above the WHO cut-off	HR 1.54 (0.91, 2.60)	*A Hb level 0–0.99 g/dL above the WHO cut-off is not associated with an increased risk of mortality* P=NR
WHO-specific criteria for anaemia				
12-year all-cause mortality (N=1790)	Anaemia (WHO) with nutrient deficiency	No anaemia	HR 1.73 (1.15, 2.60)	*WHO-defined anaemia with nutrient deficiency is significantly associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=1743)	Anaemia (WHO) with eGFR < 60 mL/min/1.73 m^2	No anaemia	HR 1.14 (0.68, 1.93)	*WHO-defined anaemia with eGFR < 60 mL/min/1.73 m^2 is not associated with an increased risk of mortality* P=NR

12-year all-cause mortality (N=1734)	Anaemia (WHO) with chronic inflammation	No anaemia	HR 2.48 (1.22, 5.05)	*WHO-defined anaemia with chronic inflammation is significantly associated with an increased risk of mortality* *P=NR*
12-year all-cause mortality (N=1731)	Anaemia (WHO) with eGFR < 60 mL/min/1.73 m^2 and chronic inflammation	No anaemia	HR 1.64 (0.86, 3.14)	*WHO-defined anaemia with eGFR < 60 mL/min/1.73 m^2 and chronic inflammation is not associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=1748)	Anaemia (WHO) but unexplained	No anaemia	HR 1.61 (0.97, 2.67)	*WHO-defined anaemia of an unexplained cause is not associated with an increased risk of mortality* *P=NR*
Ethnicity-specific criteria for anaemia				
12-year all-cause mortality (N=1764)	Anaemia (ethnicity-specific)[a] with nutrient deficiency	No anaemia	HR 1.53 (0.99, 2.04)	*Ethnicity-specific anaemia with nutrient deficiency is not associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=1716)	Anaemia (ethnicity-specific)[a] with eGFR < 60 mL/min/1.73 m^2	No anaemia	HR 1.43 (0.94, 2.16)	*Ethnicity-specific anaemia with eGFR < 60 mL/min/1.73 m^2 is not associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=1696)	Anaemia (ethnicity-specific)[a] with chronic inflammation	No anaemia	HR 2.40 (1.28, 4.51)	*Ethnicity-specific anaemia with chronic inflammation is significantly associated with an increased risk of mortality* *P=NR*

12-year all-cause mortality (N=1700)	Anaemia (ethnicity-specific)[a] with eGFR < 60 mL/min/1.73 m^2 and chronic inflammation	No anaemia	HR 1.66 (0.96, 2.88)	*Ethnicity-specific anaemia with eGFR < 60 mL/min/1.73 m^2 and chronic inflammation is not associated with an increased risk of mortality* P=NR
12-year all-cause mortality (N=1722)	Anaemia (ethnicity-specific)[a] but unexplained	No anaemia	HR 1.73 (1.08, 2.79)	*Ethnicity-specific anaemia of an unexplained cause is significantly associated with an increased risk of mortality* *P=NR*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a community-dwelling population aged ≥ 65 years.				
Applicability				
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that "the haemoglobin threshold below which mortality rises significantly is a full g/dL lower in non-Hispanic blacks than in non-Hispanic whites and Mexican Americans." They suggest that a revised definition of anaemia is needed that takes race into account. They note that the limitations of the study are (i) that Hb was assessed only on a single occasion; and (ii) that there weren't enough racial/ethnic minority participants to further stratify by sex, although analyses were adjusted for sex. An additional limitation identified by this review is that there may have been insufficient numbers of racial/ethnic minority participants in the study, which may have led to insufficient power to detect statistically significant differences in some analyses. The authors note the strengths of their study are that the sample is representative of community-dwelling older adults in the US, that follow-up was for a long period, and that the subjects were well-characterised, allowing for adjustment for multiple potential confounders as well as classification of anaemia by subtype.				

BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported; US, United States of America; WHO, World Health Organisation.

[a] Hb < 12.4 g/dL and 13.4 g/dL in non-Hispanic white women and men, respectively; <11.3 g/dL and <12.3 g/dL in non-Hispanic black women and men, respectively; <12.2 g/dL and <13.2 g/dL in Mexican American women and men, respectively.

STUDY DETAILS: Cohort study		
Citation		
Penninx et al (2006) Anemia in old age is associated with increased mortality and hospitalization. Journal of Gerontology 61A(5): 484–479.		
Affiliation/Source of funds		
VU University School of Medicine, Amsterdam, the Netherlands; University of Florida, Gainesville, US; Ortho Biotech Products, Bridgewater, US; National Institute on Aging, Bethesda, US. Supported by the National Institute on Aging and Ortho Biotech products.		
Study design	Level of evidence	Location/setting
Prospective, community-based cohort study	Level II	Community/US

Risk factor/s assessed	Potential confounding variables measured
Anaemia (WHO) and Hb levels	Age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.
Population characteristics (including size)	
Community-dwelling adults aged ≥ 65 years in East Boston, Massachusetts; New haven, Connecticut; and Iowa and Washington counties in rural Iowa; mean age 78.2 years, 64.4% female. N=3607	
Length of follow-up	Outcomes measured
Mean 4.1 years	Mortality, hospitalisation (not shown here)
Method of analysis	
Cox's proportional hazards models were used to evaluate the association of anaemia and Hb levels with time to death.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: Prospective, community-based cohort study; only 3607 were included in the analysis due to lack of blood collection at baseline (visit 6 over overarching cohort study); no details provided on subjects who did not have blood collected; analysis adjusted for variables shown to be (borderline) associated with anaemia in univariate analyses; mortality data collected via proxies, obituaries in local newspapers and the National Death Index; mean 4.1 years follow-up.	
RESULTS	

Population	With risk factor		Without risk factor	
Available	451		3156	
Analysed	451		3156	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (N=3607)	Anaemia (WHO)	No anaemia	RR 1.63 (1.37, 1.95)	*Anaemia is an independent risk factor for mortality* P<0.001
Mortality (N=1538) Without baseline disease	Anaemia (WHO)	No anaemia	RR 2.12 (1.48, 3.04)	*Anaemia is an independent risk factor for mortality in subjects <u>without baseline disease</u>* P<0.001
Mortality (N=2069)	Anaemia (WHO)	No anaemia	RR 1.43 (1.16, 1.76)	*Anaemia is an independent risk factor for mortality in subjects <u>with baseline disease</u>* P=0.001

0–2 year mortality (N=3607)	Anaemia (WHO)	No anaemia	RR 1.63 (1.23, 2.17)	*Anaemia is an independent risk factor for mortality during 0–2 years follow-up* P=0.001
2–4 year mortality (N=3607)	Anaemia (WHO)	No anaemia	RR 1.51 (1.19, 1.92)	*Anaemia is an independent risk factor for mortality during 2–4 years follow-up* P=0.001
Mortality (N=NR)	Hb ≥ 1 g/dL below the WHO cut-off	Hb 1.1–2 g/dL above the WHO cut-off	RR 1.91 (1.44, 2.53)	*Hb ≥ 1 g/dL below the WHO cut-off is an independent risk factor for mortality compared with Hb 1.1–2 g/dL above the WHO cut-off* P=NR
Mortality (N=NR)	Hb 0–0.9 g/dL below the WHO cut-off	Hb 1.1–2 g/dL above the WHO cut-off	RR 1.66 (1.30, 2.12)	*Hb 0–0.9 g/dL below the WHO cut-off is an independent risk factor for mortality compared with Hb 1.1–2 g/dL above the WHO cut-off* P=NR
Mortality (N=NR)	Hb 0.1–1.0 g/dL above the WHO cut-off	Hb 1.1–2 g/dL above the WHO cut-off	RR 1.32 (1.08, 1.60)	*Hb 0.1–1.0 g/dL above the WHO cut-off is an independent risk factor for mortality compared with Hb 1.1–2 g/dL above the WHO cut-off* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population aged ≥ 65 years.				
Applicability				
This study was conducted in three regions in the US. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that "anaemia defined according to the Who criteria was found to be significantly associated with increased mortality and hospitalization". They also note that when subgroup analyses of different patient populations and during different timepoints were performed, the results remained significant. No limitations were reported in the discussion.				

BMI, body mass index; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

STUDY DETAILS: Cohort study
Citation

Riva et al (2009) Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anemia population-based study. Haematologica 94(1): 22–28.		
Affiliation/Source of funds		
Instituto di Richerche Farmacologiche "Mario Negri", Milan; Ospedale degli Infermi, Biella; Local health Authority, ASL, BI, Biella, Italy. Supported by a research grant from Amgen Italy. It is reported that the sponsor played no part in the research or the decision to publish.		
Study design	Level of evidence	Location/setting
Prospective population-based cohort	Level II	Italy/population-based
Risk factor/s assessed	Potential confounding variables measured	
Mild anaemia (WHO and other definition)	Model 3: age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation. Model 4: age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation.	
Population characteristics (including size)		
Residents of Biella, Italy aged 65–84 years. Participants (N=4501); mean age 73.6 years; female ~60%. All residents with a CBC available (ie, includes non-participants; N=7536): mean age ~74 years; female ~60%.		
Length of follow-up	Outcomes measured	
Up to 3.5 years	Mortality, hospitalisation.	
Method of analysis		
Used Cox proportional-hazards regression models.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Prospective, population-based cohort study; of 10,110 residents in Biella, Italy, 4,501 agreed to participate; however, Hb data were available for an additional 3,035 individuals so analyses were conducted on two population: (i) participants and (ii) non-participants with available Hb data; analysis of participants conducted using different models including different confounders; analysis of participant an non-participant data adjusted for only age and sex; up to 3.5 years follow-up. Quality downgraded due to difficulty determining number of subjects included in subgroup analyses.		
RESULTS		
Population	With risk factor	Without risk factor
Available	N=4501 (participant); N=7536 (participant + non-participant with CBC data available)	
Analysed	N=313 (mild anaemia only; participant) N=716 (mild anaemia only; participant + non participant with CBC)	N=4157 (participant) N=6690 (participant + non participant with CBC)

Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Participant population				
0 to 2-year mortality (N=4470)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 1.84 (1.14, 2.87)	*Mild anaemia is an independent risk factor for mortality* P=NR
Adjusted for: age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation.				
0 to 2-year mortality (N=4470)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 2.01 (1.25, 3.09)	*Mild anaemia is an independent risk factor for mortality* P=NR
Adjusted for: age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation.				
2 to 3.5-year mortality (N=4470)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 1.88 (1.20, 2.85)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation.				
2 to 3.5-year mortality (N=4470)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 1.96 (1.26, 2.95)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation.				
0 to 3.5-year mortality (N=4470)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 1.86 (1.34, 2.53)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation.				
0 to 3.5-year mortality (N=4470)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 1.98 (1.44, 2.67)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation.				
0 to 3.5-year mortality (N=NR)	Mild anaemia of chronic disease	No anaemia	HR 5.44 (3.53, 8.06)	*Mild anaemia of chronic disease is an independent risk factor for mortality*
Fully adjusted				
0 to 3.5-year mortality (N=NR)	Mild anaemia of chronic disease (excl β-thalassemia minor)	No anaemia	HR 2.18 (1.56, 2.99)	*Mild anaemia of chronic disease (excluding β-thalassemia minor) is an independent risk factor for mortality*

Fully adjusted				
Participant + non-participant population with CBC				
60-day to 2-year mortality (N=7536)	Anaemia (WHO)	No anaemia	HR 3.43 (2.77, 4.22)	*Anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
60-day to 2-year mortality (N=7536)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 2.98 (2.36, 3.73)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
60-day to 2-year mortality (N=7536)	Mild anaemia (women: Hb 10.0–12.1 g/dL; men: Hb 10.0–13.1 g/dL)	No anaemia	HR 2.65 (2.12, 3.29)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
2 to 3.5-year mortality (N=7536)	Anaemia (WHO)	No anaemia	HR 2.23 (1.71, 2.86)	*Anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
2 to 3.5-year mortality (N=7536)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 2.16 (1.64, 2.81)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
2 to 3.5-year mortality (N=7536)	Mild anaemia (women: Hb 10.0–12.1 g/dL; men: Hb 10.0–13.1 g/dL)	No anaemia	HR 2.03 (1.57, 2.60)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
60 day to 3.5-year mortality (N=7536)	Anaemia (WHO)	No anaemia	HR 2.80 (2.38, 3.29)	*Anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
60 day to 3.5-year mortality (N=7536)	Mild anaemia (women: Hb 10.0–11.9 g/dL; men: Hb 10.0–12.9 g/dL)	No anaemia	HR 2.54 (2.14, 3.03)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				
60 day to 3.5-year mortality (N=7536)	Mild anaemia (women: Hb 10.0–12.1 g/dL; men: Hb 10.0–13.1 g/dL)	No anaemia	HR 2.32 (1.97, 2.74)	*Mild anaemia is an independent risk factor for mortality*
Adjusted for: age and sex.				

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to an elderly population aged 65–84.
Applicability
This study was conducted in a single municipality in Italy. The results of this study are likely to be applicable to the Australian setting.
Comments
The authors conclude that "mild grade anemia was found to be prospectively associated with clinically relevant outcomes such as increased risk of hospitalization and all-cause mortality". Based on the results including study participants and non-participants with CBC data available, the level of risk may be underestimated in participants, which is what has been discussed in a number of other included studies. The authors note a number of limitations of their study including (i) the limited geographic region assessed; (ii) self-report of chronic disease (although they note other studies say this might not be an issue); and (iii) potential residual confounding. While the low participation rate may have been an issue, the ability to analyse a much wider population due to on-file CBC data in non-participants most likely accounts for this.

BMI, body mass index; CBC, complete blood count; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported; WHO, World Health Organisation.

STUDY DETAILS: Cohort study				
Citation				
Thein et al (2009) Diminished quality of life and physical function in community-dwelling elderly with anemia. Medicine (Baltimore) 88(2): 107–114.				
Affiliation/Source of funds				
Institute for Advanced Studies in Aging and Geriatric Medicine, Washington; National Institute on Aging, Baltimore; University of Chicago Hospitals, Chicago; University of South Florida, Sarasota; University of Utah School of Medicine, Salt lake City; Amgen Inc, Thousand Oaks; US.				
Study design	Level of evidence		Location/setting	
Prospective cross-sectional survey	Level II		Outpatient/US	
Risk factor/s assessed		Potential confounding variables measured		
Anaemia (Hb level)		Age, sex, race and co-morbid conditions (diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions).		
Population characteristics (including size)				
Outpatients aged ≥ 65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months; mean age 76.8 years, 64% female. N=328				
Length of follow-up		Outcomes measured		
None (cross-sectional)		Functional/performance status (SF-36, FACIT-An, IADL)		
Method of analysis				
ANCOVA adjusting for various potential confounding variables.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Cross-sectional survey with prospective collection of Hb and functional/performance status data and retrospective collection of potential confounding variable data; five subjects with missing Hb data excluded from analysis (no details of patients provided); analysis adjusted for a number of known potential confounders; no details on collection of data in terms of trained personnel or blinding of Hb status.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	333			
Analysed	328			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
SF-36 – Physical Component Score (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	39.2 ± 1.1 vs 45.6 ± 1.4	*Hb < 12 g/dL is an independent risk factor for reduced SF-36 Physical Component Score compared with Hb ≥ 15 g/dL* P<0.001

SF-36 – Physical Component Score (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		39.2 ± 1.1; 42.3 ± 1.0; 43.7 ± 1.0; 44.3 ±1.1; 45.6 ± 1.4	*Declining Hb level is an independent risk factor for declining SF-36 Physical Component Score* P trend=0.002
SF-36 – Mental Component Score (N=109)	Hb categories < 12 g/dL	Hb ≥ 15 g/dL	51.6 ± 1.2 vs 56.1 ± 1.5	*Hb < 12 g/dL is an independent risk factor for reduced SF-36 Mental Component Score compared with Hb ≥ 15 g/dL* P<0.05
SF-36 – Mental Component Score (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		51.6 ± 1.2; 53.4 ± 1.1; 54.1 ± 1.1; 52.8 ±1.2; 56.1 ± 1.5	*Declining Hb level is <u>not</u> an independent risk factor for declining SF-36 Mental Component Score* P trend=0.077
SF-36 – Physical Functioning Subscale (N=109)	Hb 12 g/dL	Hb ≥ 15 g/dL	51.4 ± 3.3 vs 66.6 ± 4.2	*Hb < 12 g/dL is an independent risk factor for reduced SF-36 Physical Functioning Subscale score compared with Hb ≥ 15 g/dL* P<0.001
SF-36 – Physical Functioning Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		51.4 ± 3.3; 62.2 ± 3.0; 63.2 ± 2.9; 66.9 ±3.2; 66.6 ± 4.2	*Declining Hb level is an independent risk factor for declining SF-36 Physical Functioning Subscale score* P=0.002
SF-36 – Role Physical Subscale (N=109)	Hb 12 g/dL	Hb ≥ 15 g/dL	48.9 ± 5.0 vs 77.2 ± 6.4	*Hb < 12 g/dL level is an independent risk factor for reduced SF-36 Role Physical Subscale score compared with Hb ≥ 15 g/dL* P<0.001
SF-36 – Role Physical Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		48.9 ± 5.0; 52.2 ± 4.6; 64.2 ± 4.4; 61.7 ± 5.0; 77.2 ± 6.4	*Declining Hb level is an independent risk factor for declining SF-36 Role Physical Subscale score* P=0.001

SF-36 – Body Pain Subscale (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	59.3 ± 2.9 vs 73.4 ± 3.7	*Hb < 12 g/dL is an independent risk factor for reduced SF-36 Body Pain Subscale score compared with Hb ≥ 15 g/dL* P<0.001
SF-36 – Body Pain Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		59.3 ± 2.9; 64.9 ± 2.7; 67.2 ± 2.5; 65.1 ± 2.8; 73.4 ± 3.7	*Declining Hb level is an independent risk factor for declining SF-36 Body Pain Subscale score* P=0.011
SF-36 – General Health Subscale (N=109)	Hb 12 g/dL	Hb ≥ 15 g/dL	58.3 ± 2.4 vs 78.7 ± 3.1	*Hb < 12 g/dL is an independent risk factor for reduced SF-36 General Health Subscale score compared with Hb ≥ 15 g/dL* P<0.001
SF-36 – General Health Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		58.3 ± 2.4; 66.6 ± 2.3; 67.0 ± 2.1; 70.1 ± 2.4; 78.7 ± 3.1	*Declining Hb level is an independent risk factor for declining SF-36 General Health Subscale score* P<0.001
SF-36 – Vitality Subscale (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	50.6 ± 2.8 vs 66.7 ± 3.6	*Hb < 12 g/dL is an independent risk factor for reduced SF-36 Vitality Subscale score compared with Hb ≥ 15 g/dL* P<0.001
SF-36 – Vitality Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		50.6 ± 2.8; 57.1 ± 2.6; 55.2 ± 2.5; 57.1 ± 2.8; 66.7 ± 3.6	*Declining Hb level is an independent risk factor for declining SF-36 Vitality Subscale score* P=0.005
SF-36 – Social Functioning Subscale (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL)	76.5 ± 2.9 vs 90.5 ± 3.7	*Hb < 12 g/dL is an independent risk factor for reduced SF-36 Social Functioning Subscale score compared with Hb ≥ 15 g/dL* P<0.001

SF-36 – Social Functioning Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		76.5 ± 2.9; 82.2 ± 2.7; 84.5 ± 2.6; 84.9 ± 2.9; 90.5 ± 3.7	*Declining Hb level is an independent risk factor for declining SF-36 Social Functioning Subscale score* P=0.005
SF-36 – Role Emotional Subscale (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	70.1 ± 4.4 vs 80.2 ± 5.5	*Hb < 12 g/dL is not an independent risk factor for reduced SF-36 Role Emotional Subscale score compared with Hb ≥ 15 g/dL* P≥0.05
SF-36 – Role Emotional Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		70.1 ± 4.4; 70.6 ± 4.0; 85.3 ± 3.8; 81.2 ± 4.3; 80.2 ± 5.5	*Declining Hb level is an independent risk factor for declining SF-36 Role Emotional Subscale score* P=0.022
SF-36 – Mental Health Subscale (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	74.1 ± 2.2 vs 85.3 ± 2.8	*Hb < 12 g/dL level is an independent risk factor for reduced SF-36 Mental Health Subscale score compared with Hb ≥ 15 g/dL* P<0.001
SF-36 – Mental Health Subscale (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		74.1 ± 2.2; 80.0 ± 2.1; 78.5 ± 2.0; 75.7 ± 2.2; 85.3 ± 2.8	*Declining Hb level is not an independent risk factor for declining SF-36 Mental Health Subscale score* P=0.070
FACIT-Anaemia score (N=109)	Hb 12 g/dL	Hb ≥ 15 g/dL	46.4 ± 1.1 vs 51.3 ± 1.4	*Hb < 12 g/dL is an independent risk factor for reduced FACIT-Anaemia score compared with Hb ≥ 15 g/dL* P<0.001
FACIT-Anaemia score (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		46.4 ± 1.1; 47.8 ± 1.0; 48.0 ± 1.0; 48.5 ± 1.1; 51.3 ± 1.4	*Declining Hb level is an independent risk factor for declining FACIT-Anaemia score* P=0.017

FACIT-Fatigue score (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	35.8 ± 1.2 vs 41.1 ± 1.5	*Hb < 12 g/dL is an independent risk factor for reduced FACIT-Fatigue score compared with Hb ≥ 15 g/dL* P<0.001
FACIT-Fatigue score (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		35.8 ± 1.2; 37.9 ± 1.1; 38.4 ± 1.1; 38.5 ± 1.2; 41.1 ± 1.5	*Declining Hb level is an independent risk factor for declining FACIT-Fatigue score* P=0.015
FACIT-Non-fatigue score (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	22.5 ± 0.4 vs 23.0 ± 0.5	*Hb < 12 g/dL is <u>not</u> an independent risk factor for reduced FACIT-Non-fatigue score compared with Hb ≥ 15 g/dL* P≥0.05
FACIT-Non-fatigue score (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		22.5 ± 0.4; 22.3 ± 0.4; 21.9 ± 0.4; 22.3 ± 0.4; 23.0 ± 0.5	*Declining Hb level is <u>not</u> an independent risk factor for declining FACIT-Fatigue score* P=0.699
IADL (N=109)	Hb < 12 g/dL	Hb ≥ 15 g/dL	2.0 ± 0.3 vs 0.6 ± 0.4	*Hb < 12 g/dL level is an independent risk factor for increased IADL score compared with Hb ≥ 15 g/dL* P<0.001
IADL (N=328)	Hb categories (< 12 g/dL; 12.0–12.9 g/dL; 13.0–13.9 g/dL; 14.0–14.9 g/dL; ≥ 15 g/dL)		2.0 ± 0.3; 1.1 ± 0.3; 1.0 ± 0.2; 1.3 ± 0.3; 0.6 ± 0.4	*Declining Hb level is an independent risk factor for increasing IADL score* P=0.012
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a community-dwelling outpatient population aged ≥ 65 years				
Applicability				
This study was conducted in the US. The results of this study are likely generalisable to the Australian setting.				
Comments				
The authors conclude that "anemia was independently associated with clinically significant impairments in multiple domains of health-related quality of life, especially in measures of functional limitation. Mildly low hemoglobin levels, even when above the WHO anemia threshold, were associated with significant declines in quality of life among the elderly". A number of limitations are noted including (i) the cross-sectional nature of the study; (ii) the lack of generalisability to other racial groups; and (iii) the possibility of residual confounding.				

ANCOVA, analysis of covariance; BCC, basal cell carcinoma; dL, decilitre; FACIT, Functional Assessment of Chronic Illness Therapy; g, grams; Hb, haemoglobin; IADL, Instrumental Activities of Daily Living Scale; SF-36, Short Form (36) Health Survey; USA, United States of America.

STUDY DETAILS: Cohort study				
Citation				
Zakai et al (2005) A prospective study of anaemia status, haemoglobin concentration and mortality in an elderly cohort. Archives of Internal Medicine 165: 2214–2220.				
Affiliation/Source of funds				
University of Vermont College of Medicine, Burlington, US; Fletcher Allen Health Care, Burlington, US; Brown University, Providence, US; University of Washington, Seattle, US; University of California, Sacramento/San Francisco, US; Johns Hopkins Center on Aging and Health, Baltimore, US; University of Pittsburgh, Pittsburgh, US. Funded by the National Heart, Lung and Blood Institute. The sponsor was involved in the design and conduct of the study and approval of the manuscript.				
Study design	Level of evidence		Location/setting	
Prospective, community-based cohort	Level II		US/community	
Risk factor/s assessed		Potential confounding variables measured		
Anaemia (WHO) and Hb (quintiles)		Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.		
Population characteristics (including size)				
Community-dwelling (non-institutionalised) men and women aged ≥ 65 years; identified via Medicare eligibility lists; mean age ~ 73 years. N=5797				
Length of follow-up		Outcomes measured		
Mean 11.2 years		Mortality (all-cause, cardiovascular and non-cardiovascular).		
Method of analysis				
Staged Cox proportional-hazards models were used to assess the independent association of baseline haemoglobin quintiles or anaemia with subsequent mortality.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective, community-based cohort study; of those screened, 9.6% were ineligible to participate and 57.3% of those eligible enrolled; of 5888 participants, 5797 had baseline haemoglobin determined (98.5%); no discussion of characteristics of those who did not enrol is included; analysis adjusted for a number of confounders; follow-up a mean of 11.2 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	5888			
Analysed	498		5299	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value

All-cause mortality (N=2300)	Quintile 1 (female: Hb ≤ 12.6 g/dL; male: Hb ≤ 13.7 g/dL)	Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	HR 1.33 (1.15, 1.54)	*Anaemia (Quintile 1) is an independent risk factor for all-cause mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				
Cardiovascular mortality (N=2300)	Quintile 1 (female: Hb ≤ 12.6 g/dL; male: Hb ≤ 13.7 g/dL)	Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	HR 1.17 (0.94, 1.46)	*Anaemia (Quintile 1) is not an independent risk factor for cardiovascular mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				
Non-cardiovascular mortality (N=2300)	Quintile 1 (female: Hb ≤ 12.6 g/dL; male: Hb ≤ 13.7 g/dL)	Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	HR 1.48 (1.23, 1.79)	*Anaemia (Quintile 1) is an independent risk factor for non-cardiovascular mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				
All-cause mortality (N=2226)	Quintile 2 (female: Hb 12.7 to 13.2 g/dL; male: Hb 13.8 to 14.4 g/dL)	Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	HR 1.15 (0.99, 1.33)	*Anaemia (Quintile 2) is not an independent risk factor for all-cause mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				
All-cause mortality (N=2278)	Quintile 3 (female: Hb 13.3 to 13.8 g/dL; male: Hb 14.5 to 15.0 g/dL)	Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	HR 1.03 (0.89, 1.20)	*Anaemia (Quintile 3) is not an independent risk factor for all-cause mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				
All-cause mortality (N=5797)	Anaemia (WHO)	No anaemia	HR 1.38 (1.19, 1.59)	*Anaemia (WHO) is an independent risk factor for all-cause mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				
Cardiovascular mortality (N=5797)	Anaemia (WHO)	No anaemia	HR 1.20 (0.96, 1.51)	*Anaemia (WHO) is not an independent risk factor for cardiovascular mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				

Non-cardiovascular mortality (N=5797)	Anaemia (WHO)	No anaemia	HR 1.53 (1.28, 1.84)	*Anaemia (WHO) is an independent risk factor for non-cardiovascular mortality* *P=NR*
Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.				
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a community-dwelling (non-institutionalised) population aged ≥ 65 years.				
Applicability				
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that a "lower haemoglobin concentration was independently associated with mortality in this elderly cohort". They note a number of limitations of their study including the population examined (they note that a community-dwelling cohort may underestimate the prevalence of anaemia as it is more prevalent in the elderly population in long-term care facilities) and the lack of data on the aetiology of anaemia.				

CI, confidence interval; dL, decilitre; FVC, forced vital capacity; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported; US, United States of America; WHO, World Health Organisation.

Cancer

Level I/III evidence

STUDY DETAILS: SR/MA		
Citation		
Caro JJ, Salas M, Ward A, Goss G (2001) Anemia as an independent prognostic factor for survival in patients with cancer. Cancer 91: 2214–2221.		
Affiliation/Source of funds		
McGill University, Canada; Caro Research, US; Ottawa Regional Cancer Center, Canada. Supported in part by an unrestricted grant from Janssen Ortho, Inc.		
Study design	Level of evidence	Location/setting
Systematic review of literature. Includes data from 39 cohort studies, 19 RCTs and 2 case-referent studies.	Level I (aetiology)	Various
Intervention/risk factor	Comparator	
Anaemia (present or Hb levels; dependant on each authors individual definition and varied across studies from <8.5–14.0 g/dL)	No anaemia (not present or different Hb levels)	
Population characteristics		
Diagnosis of cancer (accepted the authors' definitions for each malignancy); no details on included patients in the individual included studies provided.		
Length of follow-up	Outcomes measured	

No reported		Mortality		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Reasonable search strategy but only Medline searched. No quality assessment of individual studies included. No characteristics of individual studies reported. Likely heterogeneity noted but not assessed.				
RESULTS				
Outcome No. trials (No. patients)	Anaemia n/N (%)	No anaemia n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Any cancer				
Mortality 60 studies (N=NR)	NR	NR	uHRR 2.33 aHRR 1.65 (1.54, 1.77)	Anaemia significantly increases mortality P<0.05 *Heterogeneity NR*
Lung cancer				
Mortality 15 studies (N=NR)	NR	NR	uHRR 1.54 a HRR 1.19 (1.10, 1.29)	Anaemia significantly increases mortality P<0.05 *Heterogeneity NR*
Head and neck carcinoma				
Mortality 10 studies (N=NR)	NR	NR	uHRR 2.35 aHRR 1.75 (1.37, 2.23)	Anaemia significantly increases mortality P<0.05 *Heterogeneity NR*
Multiple myeloma				
Mortality 7 studies (N=NR)	NR	NR	uHRR 4.47 aHRR NR	P=NR *Heterogeneity NR*
Prostate carcinoma				
Mortality 6 studies (N=NR)	NR	NR	uHRR 1.78 aHRR 1.47 (1.21, 1.78)	Anaemia significantly increases mortality P<0.05 *Heterogeneity NR*
Cervicouterine carcinoma				
Mortality 5 studies (N=NR)	NR	NR	uHRR 2.61 aHRR NR	P=NR *Heterogeneity NR*
Leukaemia				
Mortality 4 studies (N=NR)	NR	NR	uHRR 2.11 aHRR NR	P=NR *Heterogeneity NR*
Lymphoma				

Mortality 3 studies (N=NR)	NR	NR	uHRR 3.74 aHRR 1.67 (1.30, 2.13)	Anaemia significantly increases mortality P<0.05 *Heterogeneity NR*
Renal carcinoma				
Mortality 2 studies (N=NR)	NR	NR	uHRR 1.90 aHRR NR	P=NR *Heterogeneity NR*
Ovarian carcinoma				
Mortality 2 studies (N=NR)	NR	NR	uHRR 1.40 aHRR NR	P=NR *Heterogeneity NR*
Colorectal carcinoma				
Mortality 2 studies (N=NR)	NR	NR	uHRR 1.83 aHRR NR	P=NR *Heterogeneity NR*
Other				
Mortality 4 studies (N=NR)	NR	NR	uHRR 1.47–1.59 aHRR NR	P=NR *Heterogeneity NR*
EXTERNAL VALIDITY				
Generalisability				
Generalisable to a population with various types of cancer. However, no details provided on population characteristics.				
Applicability				
No details provided on location of included studies but a large number of studies included. Also, no details provided on confounding factors. Possibly applicable to the Australian setting.				
Comments				
The authors conclude that ~33% of cancer patients diagnosed as anaemic, and median survival reduced by 20–43%. State that the evidence strongly suggests that anaemia is an independent predictor of survival as the published Cox proportional hazards models were adjusted for disease stage and/or severity. The criteria used to classify a patient as anaemic varied across studies and so the analysis pools the impact across a range of haemoglobin levels (<8.5–14.0 g/dL). They note that there may have been heterogeneity with regards to study populations and study design which may have influenced the results. They assessed the possibility of publication bias and couldn't find any clear evidence of it. They note that a major limitation of the study is the inability to determine whether anaemia is a cause of decreased survival or a surrogate for other adverse factors.				

aHRR, adjusted hazard rate ratio; CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; uHRR, unadjusted hazard rate ratio.

[a] 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: SR/MA
Citation
Hauser CA, Stockler MR, Tattersall MHN (2006) Prognostic factors in patients with recently diagnosed incurable cancer: a systematic review. Support Care Cancer 14:999–1011.
Affiliation/Source of funds
Royal Prince Alfred Hospital, Australia; University of Sydney, Australia. Research was supported by Derham Green Fund Research Grant.

Study design	Level of evidence	Location/setting
Systematic review of literature published between January 2000 and October 2003. Includes data from 53 studies (study type not reported)	Level I-III (aetiology)	Various

Intervention/risk factor	Comparator
Assessed various prognostic factors including host factors (gender, age, co-morbidity), tumour factors (number of disease sites, metastatic status, tumour bulk, disease-free interval, primary tumour type and primary tumour size), treatment status (treatment type, treatment response), interaction between the host, tumour and treatment (performance status, symptoms and quality of life and laboratory manifestations, which includes anaemia).	-

Population characteristics
Aged ≥ 18 years; had one or more kinds of solid tumour; median survival between 3 and 24 months

Length of follow-up	Outcomes measured
No reported	Survival time

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Poor Description: Reasonable search strategy but only Medline searched. No quality assessment of individual studies included. No characteristics of individual studies reported. No individual results reported. No pooling of results. Describes only the number of studies which showed a significant association between anaemia and survival time using univariate and multivariate analyses.

RESULTS				
Outcome No. trials (No. patients)	Anaemia n/N (%)	No anaemia n/N (%)	Results	Significance P-value Heterogeneity P value (I^2)
Any cancer				
Survival time 18 studies (N=8998)	NR	NR	10/16 (62.5%) of studies using univariate analysis showed a significant association between anaemia and survival time compared with 4/12 (33.3%) of studies using multivariate analysis	*Heterogeneity NA*

EXTERNAL VALIDITY
Generalisability
Generalisable to a population with various types of cancer. However, no details provided on population characteristics.
Applicability
No details provided on location of included studies but a large number of studies included. Also, no details provided on confounding factors. Possibly applicable to the Australian setting.
Comments
The authors conclude that factors associated with reduced survival time in cancer include co-morbidity, primary tumour site (lung), metastatic tumour site (liver, brain and visceral), disease extent, symptoms such as anorexia-cachexia syndrome, dyspnoea, pain and impaired physical well-being, performance status and laboratory tests including anaemia, thrombocytopenia, hypoalbuminaemia and elevated levels of alkaline phosphatise and lactate dehydrogenase. Anaemia was shown to be an independent risk factor in only 4 of 12 multivariate analyses; no details are provided on what factors the analyses were adjusted for in these studies.

aHRR, adjusted hazard rate ratio; CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; NA, not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; uHRR, unadjusted hazard rate ratio.

[a] 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: SR/MA		
Citation		
Knight K, Wade S, Balducci L (2004) Prevalence and outcomes of anemia in cancer: a systematic review of the evidence. Am J Med 116 (7A): 11S-26S.		
Affiliation/Source of funds		
Zynx Health, US; Moffitt Cancer Center, US. Sponsored by the National Anaemia Action Council and funded by an educational grant from Amgen, Inc.		
Study design	Level of evidence	Location/setting
Systematic review of literature. Includes data from 19 studies relating to survival/mortality and 15 studies relating to functional status. Study types not specified.	Level I-III (aetiology)	Various
Intervention/risk factor	Comparator	
Anaemia (based on each included study's definition)	No anaemia	
Population characteristics		
Cancer (type not limited)		
Length of follow-up	Outcomes measured	
Not stated	Disease progression, survival/mortality, transfusion requirement, QoL/functional status, treatment complication.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Poor Description: *Search strategy not fully described (ie, no search terms reported) ; type of studies to be included not defined a priori; study quality not assessed; characteristics of individual studies reported; only qualitative descriptions of results of individual studies. No pooling of results.*				
RESULTS				
Outcome No. trials (No. patients)	Anaemia n/N (%)	No anaemia n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Cancer				
Mortality 19 studies (N=NR)	NR	NR	NR	18/19 included studies showed an association between anaemia and decreased survival or increased mortality
Functional status 15 studies (N=NR)	NR	NR	NR	3/15 included studies a correlation was found between anaemia and QoL scores in patients not being treated for anaemia. Other studies were intervention studies.
EXTERNAL VALIDITY				
Generalisability				
Generalisable to a population with cancer.				
Applicability				
Includes a large number of studies conducted in various regions including Europe, Africa, Asia, US, Canada, UK and Sweden. Likely to be applicable to the Australian setting.				
Comments				
The authors note that while association between anaemia and some outcomes (including mortality and functional status) have been shown, the extent to which these associations are causal in not readily ascertainable from the literature. They note that the strongest evidence appears for a number of outcomes including functional status/QoL. They note a number of limitations of the evidence including the different definitions of anaemia used in different studies, as well as the difficulty in separating out the effect of anaemia from the effect of disease severity given that anaemia prevalence increases as diseases progress. Given this review has been rated as poor quality and it does not provide quantitative results from the included studies, it is most likely to be useful only as a means of identifying relevant studies, rather than as Level I evidence.				

aHRR, adjusted hazard rate ratio; CI, confidence interval; ITT, intention-to-treat; IN-CHF, Italian Network on Congestive Heart Failure registry; MA, meta-analysis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; uHRR, unadjusted hazard rate ratio; Val-HeFT, Valsartan Heart Failure Trial. .

[a] 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] 1-year mortality.

[c] < 75 years only.

STUDY DETAILS: SR/MA
Citation

Varlotto J, Stevenson MA (2005) Anemia, tumour hypoxia and the cancer patient. Int J Radiation Oncology Biol Phys 63(1): 25–36.				
Affiliation/Source of funds				
Harvard Medical School, US. Source of funding not reported.				
Study design	Level of evidence		Location/setting	
Systematic review of literature. Includes data from 19 studies which used multivariate analysis to assess the effect of anaemia as an independent variable on prognosis of cancer.	Level I-III (aetiology)		Various	
Intervention/risk factor	Comparator			
Treatment haemoglobin levels	-			
Population characteristics				
Diagnosis of cancer; no details on included patients in the individual included studies provided.				
Length of follow-up	Outcomes measured			
No reported	Mortality; tumour progression.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Reasonable search strategy but only Medline searched. Inclusion criteria specified. No quality assessment of individual studies included. Only some of the included studies relevant to this review. Individual study results briefly described. No pooling of results.				
RESULTS				
Outcome No. trials (No. patients)	Anaemia n/N (%)	No anaemia n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
*All studies evaluated treatment Hb levels				
Cervical cancer				
Grogan 1999 (N=NR)	Anaemia	AWNH ≥ 12 g/dL	NR	Average weekly nadir Hb significantly correlated with overall survival
Hong 1998 (N=NR)	Hb< 10 g/dL	No anaemia	NR	Low Hb associated with worse survival
Kagei 1998 (N=NR)	Anaemia	≥ 10.9 g/dL	NR	Improved cause specific survival
Dunst 2003 (N=NR)	Hb as a continuous outcome		NR	Low midtherapy Hb had negative impact on survival

Head and neck cancer				
Daily 2003 (N=NR)	Anaemia	Male HB ≥ 13 g/dL; female Hb ≥ 12 g/dL	NR	Hb significantly predicted cause-specific survival
Lee 1998 (N=NR)	Anaemia	Male ≥ 14.5 g/dL; female ≥ 13 g/dL	NR	Improved survival whether Hb considered as dichotomous or continuous variable
Schafer 2003 (N=NR)	Hb as a continuous outcome		NR	Overall survival improved with higher treatment Hb
T1-T2 glottic cancer				
Fein 1995 (N=NR)	Anaemia	Hb > 13 g/dL	NR	Improved survival
Lung cancer				
MacRae 2002 (N=NR)	Hb as a continuous outcome		NR	Declining Hb during treatment associated with worse survival
Langendijk 2003 (N=NR)	Hb as a continuous outcome		NR	Higher pretreatment Hb associated with better overall survival
Nasopharyngeal cancer				
Altun 2003 (N=NR)	Severe anaemia (Hb < 11 g/dL) MDHb (≥ 1.5 g/dL)	No anaemia	NR	Both severe anaemia and MDHb associated with worse survival
EXTERNAL VALIDITY				
Generalisability				
Generalisable to a population with various types of cancer. However, no details provided on population characteristics.				
Applicability				
1/11 relevant studies conducted in Australia (head and neck cancer). Remaining studies conducted in Canada, Taiwan, Japan, US, Turkey and Germany. Possibly applicable to the Australian setting.				
Comments				
The authors note that anaemia is a prevalent condition associated with cancer and its therapies. They state that while anaemic patients will benefit from transfusion and erythropoietin, studies are needed to assess the efficacy and safety of these strategies in cancer patients. This review has been judged as being of poor methodological quality and will be useful only as a source of potentially relevant Level II/III studies.				

aHRR, adjusted hazard rate ratio; ITT, intention-to-treat; CI, confidence interval; MA, meta-analysis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; uHRR, unadjusted hazard rate ratio.

[a] 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%.

Level II evidence

STUDY DETAILS: Cohort study
Citation

Armstrong et al (2010) Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clinical Cancer Research 16(1): 203–211.		
Affiliation/Source of funds		
Duke University Medical Center, Durham, US; Medical University of South Carolina, Charleston, US; Erasmus University Medical Center, Rotterdam, the Netherlands; Princess Margaret Hospital and University of Toronto, Toronto, Canada.		
Study design	Level of evidence	Location/setting
Prospective, hospital-based cohort reanalysis of a RCT	Level II	Multinational/hospital
Risk factor/s assessed	Potential confounding variables measured	
Various (including Hb < 13.0 g/dL)	Various; the following were included in the multivariable model: prechemotherapy variables including liver metastases, significant pain, > 2 metastatic sites, KPS ≤ 70, time since diagnosis, alkaline phosphatase and post-chemotherapy variables including duration of first-line therapy, number of progression factors and progression on chemotherapy.	
Population characteristics (including size)		
For entry into the initial RCT: men with documented metastatic prostatic adenocarcinoma in the face of castrate levels of serum testosterone (< 50 ng/mL), and if they had evidence of progression as defined by clinically or radiographically measurable disease or by PSA criteria. For entry into the post-hoc analysis: had to be treated with first-line chemotherapy according to protocol and develop disease progression either after completion of the planned 30 weeks of therapy or while on therapy. In addition, patients had to have non-missing data on pain, performance status, duration of therapy and metastatic sites. No baseline data provided. N=640		
Length of follow-up	Outcomes measured	
> 12 months	Post-progression survival	
Method of analysis		
Cox proportional-hazards modelling with backward manual selection of statistically significant variables was conducted.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Prospective, hospital-based cohort analysis of a RCT; of 1006 men who took part in the RCT, 789 men completed 10 cycles of chemotherapy or progressed while on treatment; of the 789 men eligible, an additional 149 were excluded from the analysis due to missing data; men excluded did differ compared with men included in the analysis; a large number of potential confounders were considered in the multivariate analysis and only those which were significant (P<0.1) were retained in the model; follow-up was sufficient as at time of analysis, 82% of subjects had died and median survival was 14.5 months.		
RESULTS		
Population	With risk factor	Without risk factor
Available	789	
Analysed	640	

Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Post-progression survival (N=640)	Anaemia (Hb < 13 g/dL)	No anaemia	HR 1.30 (1.05, 1.58)	*Anaemia is an independent risk factor for post-progression survival* P=0.012
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of men with prostate cancer progression during or following first-line chemotherapy.				
Applicability				
This was a multicentre study conducted in Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Finland, France, Germany, Hungary, Italy, Lebanon, the Netherlands, Poland, Russia, Slovak Republic, South Africa, Spain, Sweden, United Kingdom and the United States. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors note that type of chemotherapy was not significant when used in the model and so was subsequently excluded as a variable. Other independent predictors of post-progression survival included significant pain, > 2 metastatic sites, time since diagnosis, alkaline phosphatase, duration of first-line therapy, no of progression factors and progression while on chemotherapy. The authors note a number of limitations of their study including that the RCT was not specifically designed to study the postchemotherapy disease state and the fact that post-treatment progression was up to the treating physician.				

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; KPS, Karnofsky performance score; PSA, prostate-specific antigen; RCT, randomised controlled trial; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Beer et al (2006) The prognostic value of haemoglobin change after initiating androgen-deprivation therapy for newly diagnosed metastatic prostate cancer: a multivariate analysis of Southwest Oncology Group Study 8894. Cancer 107: 489–496.		
Affiliation/Source of funds		
Oregon Health and Science University, Portland; Southwest Oncology Group Statistical Center, Seattle; University of Michigan Comprehensive Cancer Center, Ann Arbor; University of Colorado Health Science Center, Denver; US.		
Study design	Level of evidence	Location/setting
Prospective, hospital-based cohort analysis of a RCT	Level II	US/hospital

Risk factor/s assessed	Potential confounding variables measured
Haemoglobin	Race, PSA, bone pain, performance status, extensive disease, age, prior radiotherapy, radical prostatectomy, Gleason score, flutamide treatment, baseline Hb, 3-month change in Hb, African American baseline Hb.
Population characteristics (including size)	

Men with histologically proven diagnosis of adenocarcinoma of the prostate with bone or distant soft tissue metastases; age 69.6 years. N=817			
Length of follow-up	Outcomes measured		
> 2 years	Overall survival and progression-free survival		
Method of analysis			
The association between haemoglobin and time-to-event outcomes were evaluated using proportional hazards regression models with adjustment for baseline characteristics.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Good Description: Prospective, hospital-based cohort analysis of a RCT; of 1286 registered subjects, 827 were eligible had data available for all analysed variables; of these, an additional 10 were excluded as they dies or progressed within 3 months of registration; survival and progression-free survival were similar between those included and excluded from the analysis; adjusted for a number of potential confounding variables; follow-up at least 2 years.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	1286		
Analysed	817		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Overall survival (N=817)	Baseline Hb centred at 13.7 g/dL (1-unit increment)	HR 0.88 (0.83, 0.93)	*A 1 g/dL increase in Hb is independently associated with a 12% increase in survival* P<0.001
Overall survival (N=817)	3-month Hb change (1-unit decrement)	HR 1.10 (1.03, 1.16)[a]	*A 1 g/dL decrease in Hb from baseline to 3 months is independently associated with a 10% decrease in survival* *P=0.0035*
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to men with newly diagnosed prostate cancer who survived or did not progress during the first 3 months following registration in the study.			
Applicability			
This study was conducted in the US. The results of this study are likely applicable to the Australian setting.			
Comments			

The authors conclude that in addition to baseline Hb which has been previously shown to be an independent predictor of reduced survival, "a decline in HGB level after 3 months of ADT was associated with shorter survival and progression-free survival after adjusting for disease status and other baseline covariates". The authors note that the results of their study showed an effect of race; anaemic African Americans fared worse than anaemic Caucasians while African Americans with high baseline haemoglobin fared better than Caucasians with similar haemoglobin levels.

ADT, androgen-deprivation therapy; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HGB, haemoglobin; HR, hazard ratio; PSA, prostate-specific antigen; RCT, randomised controlled trial; US, United States of America.

[a] The Table shows a confidence interval of 1.03, 0.16. This is assumed to be an error and 1.16 has been shown above.

STUDY DETAILS: Cohort study				
Citation				
Cook et al (2006) Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clinical Cancer Research 12(11): 3361–3367.				
Affiliation/Source of funds				
University of Waterloo, Waterloo, Canada; Weston park Hospital, Sheffield, UK; Milton S Hershey Medical Center, Hershey, US; McMaster University, Hamilton, Canada; Novartis Pharmaceuticals Corp, East Hanover, US; Hôpital Notre-Dame, Montreal, Canada; Massachusetts General Hospital, Boston, US. Funded by Novartis Oncology and the John and Claire Bertucci Center for Genitourinary Malignancies at Massachusetts General Hospital.				
Study design	Level of evidence		Location/setting	
Prospective, hospital-based cohort analysis of a RCT	Level II		US, Argentina, Australia, Canada, France, Brazil, Germany, UK, New Zealand, Italy, Chile, Switzerland, Austria, Belgium, Peru, Sweden, Uruguay/hospital	
Risk factor/s assessed		Potential confounding variables measured		
Various (various including Hb)		Age, PSA, LDH, analgesic, BAP.		
Population characteristics (including size)				
Men with histologically confirmed prostate cancer, bone metastases and disease progression despite medical or surgical castration; mean age 71.7 years; duration of disease 5.5 years.				
Length of follow-up		Outcomes measured		
Up to 2 years		Overall survival		
Method of analysis				
Multivariable models were fit using all explanatory variables to identify those that were independently predictive. Stepwise backward elimination was carried out to determine the simplest multivariate model; only terms remaining significant at the 5% level were retained in the reduced model.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective cohort analysis of a hospital-based RCT; 592/643 potentially eligible subjects with a complete dataset were included; no comment made on any differences between the included and excluded subjects; a large number of potential confounding variables examined; follow-up up to 2 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	643			
Analysed	592			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Overall survival (N=592)	Hb dichotomised (no further details given)		RR 0.84 (0.78, 0.91)	*A low haemoglobin is independently associated with reduced survival* P<0.001

Overall survival (N=592)	Hb in quartiles (no further details given)	RR 0.84 (0.78, 0.90)	*A low haemoglobin is independently associated with reduced survival* P<0.001
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Overall survival (N=592)	Hb as a continuous variable	RR 0.84 (0.78, 0.90)	*A 1 g/dL reduction in haemoglobin is independently associated with reduced survival* P<0.001
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of men with androgen-independent prostate cancer and bone metastases.			
Applicability			
This study was conducted in the US, Canada and the UK. The results of this study are likely applicable to the Australian setting.			
Comments			
The authors conclude that "higher levels of BAP but not urinary N-telopeptide are associated with overall survival". Within their analysis they also showed that low haemoglobin was an independent predictor of shorter survival. Other independent predictors of survival were age, PSA, LDH and analgesic use. The reporting of this study is deficient; it is unclear exactly how the dichotomised and quartile levels of Hb have been compared.			

BAP, bone-specific alkaline phosphatise; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; RCT, randomised controlled trial; RR, risk ratio; UK, United Kingdom; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Halabi et al (2009) Progression-free survival as a predictor of overall survival in men with castrate-resistant prostate cancer. Journal of Clinical Oncology 27(17): 2766–2771.		
Affiliation/Source of funds		
Duke University, Durham, US; Nevada Cancer Institute, Las Vegas, US; Fred Hutchison Cancer Research center, Seattle, US; University of California, San Francisco, US. Supported in part by grants from the US Department of Defence and the National Cancer Institute.		
Study design	Level of evidence	Location/setting
Cohort analysis of data from 9 RCTs	Level II	Hospital/US
Risk factor/s assessed	Potential confounding variables measured	
Progression-free survival and biochemical progression (Hb assessed as a potential confounder)	Adjusted for known prognostic variables: progression at 3 months, age, performance status, presence of visceral disease, BMI, Gleason score, testosterone, race, prior radiotherapy, alkaline phosphatase, years since diagnosis, PSA, LDH.	

Population characteristics (including size)			
Men with prostate cancer who had progressed during androgen deprivation therapy; median age at diagnosis 71 years; 15% African American. N=1201			
Length of follow-up	Outcomes measured		
Not stated (but median survival was 17.8 months in one subgroup)	Overall survival		
Method of analysis			
The proportional hazards model was used.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: Cohort analysis of data from 9 RCTs; Data from 1296 men available but only 1201 included in analysis; no explanation given for missing subjects; analysis adjusted for a number of variables known to be prognostic for survival; ascertainment of survival status not described; follow-up not stated but given median survival shown to be up to 17.8 months in one of the subgroups, is likely to have been sufficient for this population and outcome.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	1296		
Analysed	1201		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Overall survival (N=1201)	Hb change (1 g/dL)	HR 0.91 (0.86, 0.97)	*A change in Hb of 1 g/dL is an independent risk factor for decreased survival* P=0.002
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to men with prostate cancer who have progressed during androgen therapy.			
Applicability			
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors make no conclusions regarding the association between Hb and overall survival, as Hb was only a prognostic variable included in the model. An assumption had to be made regarding the interpretation of the results; it is assumed that the "change" in Hb is actually a decrease of 1 g/dL, and that the HR of 0.91 (0.86, 0.97) relates to a decrease in survival.			

BMI, body mass index; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; RCT, randomised controlled trial; US, United States of America.

STUDY DETAILS: Cohort study				
Citation				
Köhne et al (2002) Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Annals of Oncology 13: 308–317.				
Affiliation/Source of funds				
Universitätsklinikum Carl Gustav Carus der TU-Dresden, Dresden, Germany; The Royal Marsden Hospital, Sutton, UK; Azienda Ospedaliera S. Maria, Terni, Italy; University Hospital, Uppsala, Sweden; Academisch Ziekenhuis Utrecht, Utrecht, the Netherlands; Hospital Universitario 'Reina Sofia', Cordoba, Spain; University Hospital, Vienna, Austria; Hôpital Ambroise Paré, Boulonge Cedex, France; Astra-Zeneca Pharmaceuticals, Macclesfield, UK; Laurentius Hospital, Roermond, the Netherlands; EORTC Data Center, Brussels, Belgium; Medical School Hannover, Hannover, Germany; Campus Berlin-Buch, Berlin, Germany. Funding not stated.				
Study design	Level of evidence		Location/setting	
Prospective cohort analysis of data from a number of a hospital-based RCTs and Phase II trials	Level II		Europe/hospital	
Risk factor/s assessed		Potential confounding variables measured		
Various including Hb		Unclear		
Population characteristics (including size)				
Patients treated with 5-FU for metastatic colorectal cancer; no further details provided. N=3825				
Length of follow-up		Outcomes measured		
Not stated		Overall survival		
Method of analysis				
Recursive partition and amalgamation (REPCAM) was used to analyse the relationship between the predictor variables and total survival. Univariate and multivariate analyses were undertaken.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Prospective cohort analysis of a large number of hospital-based RCTs and phase II studies; no details provided on how many subjects from each trial included in the analysis although the paper does state that 30% had missing Hb data and missing data for other variables ranged from 0% to 72%; the analysis appears to have been adjusted for a number of variables although it is unclear exactly what these were; it is unclear how long follow-up was.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	3825			
Analysed	3825			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value

Overall survival (N=3825)	Hb < 11 g/dL	Hb ≥ 11 g/dL	NR	*Hb < 11 g/dL was an independent predictor of reduced survival* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with metastatic colorectal cancer treated with 5-FU.				
Applicability				
This study was conducted in a number of European countries. The results of this study are likely applicable to the Australian setting.				
Comments				
The major aim of this study was to generate a general predictive model for survival in patients with metastatic colorectal cancer treated with 5-FU. In the process of identifying variables for the model, low Hb was identified as one of a number of independent risk factors for reduced survival. A lack of reporting of detail in this study has led to it receiving a low quality rating.				

5-FU, 5-fluorouracli; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; NR, not reported; PSA, prostate-specific antigen; RCT, randomised controlled trial; UK, United Kingdom.

STUDY DETAILS: Cohort study			
Citation			
Laurie et al (2007) The impact of anaemia on outcome of chemoradiation for limited small-cell lung cancer: a combined analysis of studies of the National Cancer Institute of Canada Clinical Trials Group. Annals of Oncology 18: 1051–1055.			
Affiliation/Source of funds			
The Ottawa Hospital Regional cancer Centre, Ottawa; National Cancer Institute of Canada Clinical Trials Group, Kingston; Princess Margaret Hospital, Toronto; British Columbia Cancer Agency, Vancouver; Canada. Funding not stated.			
Study design	Level of evidence	Location/setting	
Prospective cohort analysis of 2 hospital-based RCTs	Level II	Canada/hospital	
Risk factor/s assessed	Potential confounding variables measured		
Anaemia via different Hb measures	Gender, ECOG PS, LDH.		
Population characteristics (including size)			
Patients with NSCLC; ~ 65 years; male 64%			
Length of follow-up	Outcomes measured		
Not stated	Overall survival and local chest recurrence		
Method of analysis			
A Cox regression model, stratified by treatment arm, using stepwise procedure with a significance level of 0.1 for factors to stay, was used to study the effect of Hb level on time-to-event outcomes while adjusting for baseline prognostic factors.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			

Rating: Fair Description: Prospective cohort analysis of data from two hospital-based RCTs; all 652 subjects included in the baseline Hb analysis; the nadir Hb analysis included 633/652 subjects while the pre-PCI Hb analysis included 523/652 subjects; no comparison of patients included or excluded from the analyses is provided; a number of variables were examined for inclusion in the adjusted analysis and only 4 including Hb remained; length of follow-up is unclear.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	210		442	
Analysed	210 (baseline Hb)		442 (baseline Hb)	
	633 (nadir Hb)			
	523 (pre-PCI Hb)			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Overall survival (N=652)	Baseline anaemia (baseline Hb < 13.6 g/dL for males and < 12.0 g/dL for females)	No anaemia	HR 0.95 (0.80, 1.13)	*Baseline anaemia is not an independent risk factor for survival* P=0.57
Overall survival (N=633)	Nadir Hb < 10.0 g/dL	Nadir Hb ≥ 10.0 g/dL	HR 1.09 (0.92, 1.31)	*Nadir Hb < 10.0 g/dL is not an independent risk factor for survival* P=0.33
Overall survival (N=NR)	Hb % reduction 10–30%	Hb % reduction < 10 %	HR 0.83 (0.60, 1.14)	*Hb % reduction 10–30% is not an independent risk factor for survival* P=0.25
Overall survival (N=NR)	Hb % reduction > 30%	Hb % reduction < 10 %	HR 0.94 (0.68, 1.31)	*Hb % reduction > 30% is not an independent risk factor for survival* P=0.73
Overall survival (N=523)	Pre-PCI Hb < 10.0 g/dL	Pre-PCI Hb ≥10.0 g/dL	NR	*Pre-PCI Hb < 10.0 g/dL is not an independent risk factor for survival* P=0.31
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with non-small cell lung cancer treated with chemotherapy.				
Applicability				
This study was conducted in Canada. The results of this study are likely applicable to the Australian setting.				
Comments				

The authors conclude that while anaemia does not appear to be an independent risk factor for overall survival in this patient population, it may have different prognostic implications at diagnosis compared with during treatment. Other variables identified as independent risk factors were male gender, ECOG PS ≥ 2 and elevated LDH. It is unclear how long the follow-up period of this study was.

CI, confidence interval; dL, decilitre; ECOG PS, Eastern Cooperative Oncology Group Performance Status; g, grams; Hb, haemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer; PCI, prophylactic cranial irradiation; RCT, randomised controlled trial.

STUDY DETAILS: Cohort study				
Citation				
Mandrekar (2006) A prognostic model for advanced stage nonsmall cell lung cancer: pooled analysis of North Central Cancer Treatment Group trials. Cancer 107: 781–792.				
Affiliation/Source of funds				
Mayo Clinic, Rochester, US; Missouri Valley Cancer Center, Omaha, US; Duluth Clinic, Duluth, US; University of Mannitoba, Winnipeg, Canada; Southwest Oncology group Statistical Center, Seattle, US; University of Colorado, Denver, Colorado. Supported by a National Cancer Institute grant.				
Study design	Level of evidence		Location/setting	
Prospective, cohort analysis of pooled RCTs	Level II		US/Canada/hospital	
Risk factor/s assessed		Potential confounding variables measured		
Various including anaemia		Age, gender, ECOG PS, cancer stage, BMI, WBC.		
Population characteristics (including size)				
Patients with advanced-stage NSCLC (stage IIB with pleural effusion and stage IV); median age 64, median BMI 24.6, male 66.4%. N=782				
Length of follow-up		Outcomes measured		
Appears to be up to 2 years		Overall survival, time to progression		
Method of analysis				
The Cox proportional-hazards model was used the multivariate analysis.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Prospective cohort analysis of pooled data from nine RCTs; 1053 subjects available for analysis; only 782 of these included in the multivariate analysis; no details provided on the comparison between included and excluded subjects; results adjusted for a number of potential confounders although the authors note that there may have been many others not included due to different data collection in different trials; follow-up appears to be at least 2 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	360 (pooled)		692 (pooled)	
Analysed	277 (pooled) 170 (validation cohort)		505 (pooled) 256 (validation cohort)	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Overall survival (N=782) Meta-analysis of 9 RCTs	Anaemia (Hb < 13.2 g/dL for males and < 11.5 g/dL for females)	No anaemia	HR 1.51 (1.28, 1.78)	*Anaemia is an independent risk factor for overall survival* P<0.001

Overall survival (N=426) Validation cohort	Anaemia (Hb < 13.2 g/dL for males and < 11.5 g/dL for females)	No anaemia	HR 1.21 (0.98, 1.50)	*Anaemia is not an independent risk factor for overall survival* P=0.07
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with advanced NSCLC (Grade III with pleural effusion and Grade IV)				
Applicability				
This study was conducted in the US and Canada. The results of this study are likely generalisable to the Australian setting.				
Comments				
The results show that anaemia was a significant independent risk factor for overall survival in the pooled analysis but not the analysis of the validation cohort (although the p value was 0.07). The authors note that the Hb variable had an influential trial (HR 9.5), but that all trials showed effects in the same direction with similar magnitudes (1.1 to 1.9). Therefore, they considered including the Hb variable was justified as the heterogeneity was only quantitative. The majority of variables shown to be independent predictors of overall survival in the pooled analysis, just failed to reach statistical significant in the validation cohort analysis. The authors note a number of limitations of their study including the shorter average survival in the pooled trials compared with the validation trial, the possibility of residual confounding due to the large number of potential confounders which were not included in the analysis (eg, number and sites of metastases, smoking status and weight loss) and the differences in results in certain subgroups.				

BMI, body mass index; CI, confidence interval; dL, decilitre; ECOG PS, Eastern Cooperative Oncology Group Performance Status; g, grams; Hb, haemoglobin; HR, hazard ratio; NSCLC, non-small-cell lung cancer; RCT, randomised controlled trial; US, United States of America; WBC, white blood cell count.

STUDY DETAILS: Cohort study		
Citation		
Négrier et al (2002) Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Français d'Immunothérapie. Annals of Oncology 13: 1460–1468.		
Affiliation/Source of funds		
Centre Léon Bérard, Lyon, France; Institut Gustave Roussy, Villejuif, France; Centre René Gauducheau, nantes, France; Institut Bergonié, Bordeauz, France; Centre Claudius Regaud, Tolouse, France. Funding not stated.		
Study design	Level of evidence	Location/setting
Cohort analysis of five prospective trials	Level II	Hospital/France
Risk factor/s assessed	Potential confounding variables measured	
Various (including anaemia)	Variables with P<0.1 in univariate analysis: Inflammation, time from tumour to metastases, ECOG performance status, number of metastatic sites, neutrophils, alkaline phosphatase, liver metastasis, bone metastasis, mediastinum metastasis.	
Population characteristics (including size)		

Adults 18–80 with histologically confirmed and measurable metastatic renal cell carcinoma; mean age 58 years, 72%. N=782				
Length of follow-up	Outcomes measured			
Median 77 months	Overall survival			
Method of analysis				
Used a stepwise Cox's model.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Cohort analysis of data from five prospective trials; no details provided on patients included in/excluded from analysis, although there is a note that there was a limited number of missing values and that the highest was 13% for inflammation markers; analysis adjusted for 15 variables identified during univariate analysis; follow up median 77 months.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	352		424	
Analysed	352		424	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Overall survival (N=782)	Anaemia (Hb < 11.5 g/dL (female) or < 13.0 g/dL (male))	No anaemia (Hb ≥ 11.5 g/dL (female) or ≥ 13.0 g/dL (male))	RR 1.400 (1.167, 1.684)	*Anaemia is an independent risk factor for decreased survival* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to an adult population with metastatic renal cell carcinoma.				
Applicability				
This study was conducted in France. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that anaemia, along with a number of other variables, is a validated prognostic factor for survival in this patient group. Other prognostic factors included biological signs of inflammation, short time from renal tumour to metastases, elevated neutrophil counts, liver metastases, bone metastases, patient performance status, number of metastatic sites and alkaline phosphatase.				

CI, confidence interval; dL, decilitre; ECOG, Eastern Cooperative Oncology Group; .Hb, haemoglobin; g, grams; RR, relative risk

STUDY DETAILS: Cohort study
Citation
Nieboer et al (2005) Fatigue and relating factors in high-risk breast cancer patients treated with adjuvant standard or high-dose chemotherapy: a longitudinal study. Journal of Clinical Oncology 23(33): 8296–8304.
Affiliation/Source of funds

University of Groningen, Groningen; The Netherlands Cancer Institute, Amsterdam; Erasmus Medical Center/Daniel den Hoed Cancer Center, Rotterdam; University Medical Canter Nijmegen St. Radboud, Nijmegen; Free University Hospital, Amsterdam; University Medical Center, Utrecht; University Hospital, Maastricht; The Netherlands.				
Study design	Level of evidence		Location/setting	
Cross-sectional analysis of a RCT	Level II		The Netherlands/hospital	
Risk factor/s assessed		Potential confounding variables measured		
Various including anaemia (≤ 12 g/dL)		Adjusted for: mental health score, muscle pain, joint pain, treatment group, menopausal status.		
Population characteristics (including size)				
Women aged < 56 years with stages II and III breast cancer and ≥ 4 positive axillary lymph nodes, a normal chest x-ray, normal bone-scan, normal liver sonogram, a WHO performance status of 0 or 1, and no prior treatment other than surgery who were disease-free until at least 3 years after surgery; mean age ~ 45.5 years.				
Length of follow-up		Outcomes measured		
3 years		Fatigue (defined as an SF-36 Vitality score ≤ 46).		
Method of analysis				
Multiple logistic regression with fatigue as the dependent variable and other variables (including anaemia) as independent variables.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Cross-sectional cohort analysis of data from a RCT; of 838 potentially eligible, 804 completed one or more QoL questionnaires; at 3 years follow-up 430 were available and disease-free; 426 available for analysis of Hb at baseline and < 300 by year 3; adjusted for a number of potential confounders but a number of other known confounders have not been assessed; outcome assessment subjective and unclear if patients aware of haemoglobin status so potential for bias.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	430			
Analysed	426			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Fatigue (N=426) Baseline	Hb ≤ 12 g/dL	Hb > 12 g/dL	OR 3.5 (1.7, 7.1)	*Hb ≤ 12 g/dL is an independent risk factor for fatigue compared with Hb > 12 g/dL at randomisation.* P=0.001
Fatigue (N=410) 1 year	Hb ≤ 12 g/dL	Hb > 12 g/dL	OR 1.1 (0.5, 2.2)	*Hb ≤ 12 g/dL is not an independent risk factor for fatigue compared with Hb > 12 g/dL at 1 year.* P=0.789

Fatigue (N=394) 2 year	Hb ≤ 12 g/dL	Hb > 12 g/dL	OR 0.9 (0.7, 2.0)	*Hb ≤ 12 g/dL is not an independent risk factor for fatigue compared with Hb > 12 g/dL at 2 years.* P=0.724
Fatigue (N=292) 3 year	Hb ≤ 12 g/dL	Hb > 12 g/dL	OR 2.0 (0.7, 5.5)	*Hb ≤ 12 g/dL is not an independent risk factor for fatigue compared with Hb > 12 g/dL at 3 years.* P=0.176
EXTERNAL VALIDITY				
Generalisability				
This study is generalisable to a population of women with high-risk breast cancer who have had surgery.				
Applicability				
This study was conducted in the Netherlands. The results of this study may be applicable to the Australian setting.				
Comments				
The authors note that a significant relation between anaemia and fatigue was seen only at randomisation, and not at the other follow-up periods. They also note that only 5% of all women experienced anaemia and fatigue. They state that "the fact that Hb is only a predictor at random assignment is most likely because the breast operation before random assignment is often accompanied by blood loss".				

CI, confidence interval; dL, decilitre; g, gram; Hb, haemoglobin; OR, odds ratio; RCT, randomised controlled trial; SF-36, Short Form (36) Health Survey; WHO, World Health Organisation.

STUDY DETAILS: Cohort study		
Citation		
Østerlind et al (1986) Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Research 46: 4189–4194.		
Affiliation/Source of funds		
Bispebjerg Hospital and Statistical Research Unit, Copenhagen, Denmark.		
Study design	Level of evidence	Location/setting
Cohort analysis of data from six treatment trials.	Level II	Hospital/Denmark

Risk factor/s assessed	Potential confounding variables measured
Various (including Hb level)	Analysis 1: Variables with significant influence in at least one of the disease categories: performance status, LDH, sodium, urate, sex, age, alternating regimen. Analysis 2: Variables with significant influence in at least one of the disease categories: performance status, LDH, resected patients, sodium, sex, age, alternating regimen, extensive disease.
Population characteristics (including size)	

Adults with small cell lung cancer – 443 with limited disease and 431 with extensive disease; no subjects characteristics reported.				
Length of follow-up	Outcomes measured			
18 months	Survival			
Method of analysis				
Cox's proportional hazards model was used.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Cohort analysis of six RCTs; 874 subjects included in trials, up to 778 included in analysis; no details of why subjects were missing from the analysis is reported; no details on included subjects is provided; analyses adjusted for variables shown to have significant influence; follow-up 2 years.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	208		662	
Analysed	746 (analysis 1)/778 (analysis 2)			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Survival (N=746) Analysis 1 (includes interactions)	Anaemia (Hb < 12 g/dL)	No anaemia (Hb ≥ 12 g/dL)	NR	*Anaemia is an independent risk factor for reduced survival* P<0.001
Survival (N=778) Analysis 2 (ignores interactions)	Anaemia (Hb < 12 g/dL)	No anaemia (Hb ≥ 12 g/dL)	NR	*Anaemia is an independent risk factor for reduced survival* P<0.05
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of adults with small cell lung cancer.				
Applicability				
This study was conducted in Denmark. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors note that low haemoglobin was associated with a reduced duration of survival. Other variables shown to be associated with reduced survival included poor performance status and raised lactate dehydrogenase.				

CI, confidence interval; Hb, haemoglobin; LDH, lactate dehydrogenase; NR, not reported; RCT, randomised controlled trial.

STUDY DETAILS: Cohort study
Citation

Paesmans et al (1995) Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European Lung Cancer Working Party. Journal of Clinical Oncology 13: 1221–1230.				
Affiliation/Source of funds				
Institute Jules Bordet, Bruxelles; Hôpital Civil de Charleroi, Charleroi; Centre Hospitalier de Tivoli, La Louvière; Clinique St Luc, Namur; Hôpital Saint-Pierre, Bruxelles, Belgium; Groupe Médical St Rémi, Reims; Centre Hospitalier Universitaire de Nantes, Nantes, France. Funding not stated.				
Study design	Level of evidence		Location/setting	
Cohort analysis of data from 7 RCTs	Level II		Hospital/Europe	
Risk factor/s assessed		Potential confounding variables measured		
Various (including haemoglobin level)		Variables included in the best-fit model from 23 initial variables: disease extent, KPS, WBC count, skin metastases, calcium, neutrophil, age, sex.		
Population characteristics (including size)				
Adults with non-small-cell lung cancer treated by chemotherapy; 42% aged < 60 years, 90% male. N=1052				
Length of follow-up		Outcomes measured		
Median follow-up 270 weeks (range 53–606)		Survival		
Method of analysis				
Cox regression model used for the multivariate analysis; explanatory variables selected using a stepwise forward procedure with an enter limit fixed as a significance probability of 0.05.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Cohort analysis of data from 7 RCTs; 5.6% of subjects lost to follow-up; a large number of potential confounding variables considered in the analysis; analysis adjusted for variables shown to be significant in the stepwise regression analysis; follow-up median 270 weeks.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	1111 (based on reporting of 59 subjects lost to follow-up).			
Analysed	1052			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Survival (N=1052)	Haemoglobin level < 12 g/dL and > 18 g/dL	Haemoglobin level between 12 and 18 g/dL	NR	*Haemoglobinaemia is not an independent risk factor for survival* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to adults with non-small-cell lung cancer treated with chemotherapy.				

Applicability
This study was conducted in Europe. The results of this study are likely to be applicable to the Australian setting, although it should be noted that the data was taken from trials conducted between 1980 and 1991.
Comments
The authors found that disease extent, KPS, WBC and neutrophil counts, metastatic involvement of skin, calcium, age and sex were independent predictors of survival in this patient group. While haemoglobinaemia was shown to be significant associated with survival in the univariate analysis, it was excluded from the multivariate analysis during the stepwise analysis.

CI, confidence interval; g, grams; dL, decilitre; KPS, Karnofsky performance status; NR, not reported; RCT, randomised controlled trial; WBC, white blood cell.

STUDY DETAILS: Cohort study				
Citation				
Paesmans et al (2000) Prognostic factors for patients with small-cell lung cancer: analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. Cancer 89: 523–533.				
Affiliation/Source of funds				
Institute Jules Bordet, Bruxelles; Hôpital Civil de Charleroi, Charleroi; Hôpital de Warquignies, Boussu; Clinique St Luc, Namur; Hôpital Saint-Pierre, Bruxelles, Belgium; Groupe Médical St Rémi, Reims; Centre Hospitalier Universitaire de Nantes, Nantes, France. Funding not stated.				
Study design	Level of evidence		Location/setting	
Cohort analysis of 4 RCTs	Level II		Hospital/Europe	
Risk factor/s assessed		Potential confounding variables measured		
Various (including haemoglobin level)		Variables included in the best-fit model from 21 initial variables: KPS, sex, female gender, neutrophil rate.		
Population characteristics (including size)				
Adults with small-cell lung cancer, aged < 75 years, no prior treatment; 90% male, 41% aged < 60 years. N=763				
Length of follow-up		Outcomes measured		
Median follow-up 118 months (range 1–149)		Survival and long-term survival (also tumour response, complete response and cure status).		
Method of analysis				
Multivariate analysis was performed using either multiple logistic regression or Cox regression models, with a backward forward stepwise method for the selection of covariates.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Cohort analysis of data from 4 RCTs; no details provided on patients who may have been excluded from the analysis with the exception that 7 patients were not assessed for haemoglobin; 21 potential confounding variables examined, with 4 included in the best-fit model, median follow-up 118 months.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR			
Analysed	132		624	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Survival (N=756)	Haemoglobin level < 12 g/dL and > 18 g/dL	Haemoglobin level between 12 and 18 g/dL	NR	*Haemoglobinaemia is not an independent risk factor for survival* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to an adult population with small-cell lung cancer.				
Applicability				

This study was conducted in Europe. The results of this study are likely to be applicable to the Australian setting.
Comments
The authors found that disease extent, KPS, neutrophil counts, and sex were independent predictors of survival in this patient group. While haemoglobinaemia was shown to be significant associated with survival in the univariate analysis, it was excluded from the multivariate analysis during the stepwise analysis.

CI, confidence interval, g, grams; dL, decilitre; KPS, Karnofsky performance status; NR, not reported; RCT, randomised controlled trial

STUDY DETAILS: Cohort study		
Citation		
Wisløff et al (2005) Quality of life may be affected more by disease parameters and response to therapy than by haemoglobin changes. European Journal of Haematology 75: 293–298.		
Affiliation/Source of funds		
Ullevål University Hospital, Oslo, Norway; Lidköping Hospital, Sweden; Lind University Hospital, Lund, Sweden; University of Aberdeen, Scotland.		
Study design	Level of evidence	Location/setting
Cross-sectional analysis of data from 2 prospective trials (NMSG # 4/90 and NMSG # 5/94)	Level II	Denmark, Norway and Sweden/hospital
Risk factor/s assessed	Potential confounding variables measured	
Hb as a continuous variable	Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii), extent of skeletal disease and response category (follow-up analyses only).	
Population characteristics (including size)		
Newly diagnosed patients with multiple myeloma; median age 62 (28–87), 59% male. N=745		
Length of follow-up	Outcomes measured	
Cross-sectional but measurements prior to treatment and at 12 months (when most had completed treatment)	EORTC-QLQ-30 (Physical functioning, Role functioning, Global QoL, Pain, Fatigue)	
Method of analysis		
Linear regression		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: Cross-sectional cohort analysis of data from two prospective trials; 521/583 (89%) in study 1 and 224/284 (79%) in study 2 completed the questionnaire at baseline and follow-up; no discussion of the characteristics of those who did not participate in the QoL study; analysis adjusted for a large number of potential confounding variables; subjective outcome and unclear if subjects or investigators were aware of the Hb status so potential for bias.		
RESULTS		
Population	With risk factor	Without risk factor
Available	867	

Analysed	745		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
EORTC-QLQ-30 Physical functioning (N=745) Baseline	Hb level	NR	*Hb level is not significantly associated with EORTC-QLQ-30 Physical functioning score* P=0.674
EORTC-QLQ-30 Role functioning (N=745) Baseline	Hb level	NR	*Hb level is not significantly associated with EORTC-QLQ-30 Role functioning score* P=0.989
EORTC-QLQ-30 Global QoL (N=745) Baseline	Hb level	NR	*Hb level is significantly associated with EORTC-QLQ-30 Global QoL score* P=0.041
EORTC-QLQ-30 Fatigue (N=745) Baseline	Hb level	NR	*Hb level is significantly associated with EORTC-QLQ-30 Fatigue score* P=0.001
EORTC-QLQ-30 Pain (N=745) Baseline	Hb level	NR	*Hb level is not a significantly associated with EORTC-QLQ-30 Pain score* P=0.417
EORTC-QLQ-30 Physical functioning (N=745) 12 months (after treatment)	Hb level	NR	*Hb level is not significantly associated with EORTC-QLQ-30 Physical functioning score* P=0.300
EORTC-QLQ-30 Role functioning (N=745) 12 months (after treatment)	Hb level	NR	*Hb level is not a significantly associated with EORTC-QLQ-30 Role functioning score* P=0.079
EORTC-QLQ-30 Global QoL (N=745) 12 months (after treatment)	Hb level	NR	*Hb level is significantly associated with EORTC-QLQ-30 Global QoL score* P=0.052

EORTC-QLQ-30 Fatigue (N=745) 12 months (after treatment)	Hb level	NR	*Hb level is significantly associated with EORTC-QLQ-30 Fatigue score* P=0.010
EORTC-QLQ-30 Pain (N=745) 12 months (after treatment)	Hb level	NR	*Hb level is not a significantly associated with EORTC-QLQ-30 Pain score* P=0.946
EXTERNAL VALIDITY			
Generalisability			
This study is generalisable to an adult population with multiple myeloma.			
Applicability			
This study was conducted in Denmark, Norway and Sweden. The results of this study may be generalisable to the Australian setting.			
Comments			
The authors conclude that "haemoglobin and extent of skeletal disease were both predictors for fatigue in patients with newly diagnosed multiple myeloma, but extent of skeletal disease was also associated with other important QoL scores". They also note that the small R-squares they found during the analysis suggest that < 20% of the variability in QoL scores could be explained by variability in the predictor variables and that most the variability is likely due to individual psychological factors.			

CI, confidence interval; EORTC-QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30); Hb, haemoglobin; NR, not reported; QoL, quality of life

Renal

Level I/III evidence

STUDY DETAILS: SR/MA		
Citation		
Volkova et al (2006) Evidence-based systematic literature review of hemoglobin/haematocrit and all-cause mortality in dialysis patients. American Journal of Kidney Diseases 47(1): 24–36.		
Affiliation/Source of funds		
Rollins School of Public Health, Emory University, Atlanta; Department of Epidemiology, University of California US. No specific funding but two authors were employed by Amgen Inc at the time the work started.		
Study design	Level of evidence	Location/setting
Systematic review of RCT (5) and observational study (13) evidence (includes retrospective cohort studies)	Level I/III	Various
Intervention/risk factor	Comparator	
Haemoglobin/haematocrit levels	Different levels	
Population characteristics		

Incident or prevalent patients undergoing dialysis (haemo or peritoneal).	
Length of follow-up	Outcomes measured
Various	All-cause mortality
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Good literature search; no hand-searching reported but checked search results against an existing review; no formal assessment of study quality but some studies were excluded due to poor methodology; data not pooled. Quality rating: Fair	
EXTERNAL VALIDITY	
Generalisability	
The results are generalisable to an adult population undergoing haemodialysis or peritoneal dialysis.	
Applicability	
Studies were conducted in various locations so likely to be applicable to the Australian setting.	
Comments	
The authors note that "observational studies that analysed haematocrit and/or Hb values categorically consistently showed increased mortality associated with Hb levels less than their individual reference range". However, they also note the heterogeneity of the included observational studies (in terms of populations (HD or PD), levels assessed (incident/prevalent) and covariates adjusted for (IV/EPO only reported in one).	

EPO, erythropoietin; Hb, haemoglobin; HD, haemodialysis; IV, intravenous; PD, post-dialysis; RCT, randomised controlled trial; US, United States of America.

[a] 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%.

Level II evidence

STUDY DETAILS: Cohort study		
Citation		
Abramson et al (2003) Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: The ARIC Study. Kidney International 64: 610–615.		
Affiliation/Source of funds		
Department of Medicine, Emory University School of Medicine, Atlanta, US. The ARIC study is conducted and supported by the National Heart, lung and Blood Institute in collaboration with the ARIC Study Investigators. This study was not prepared in collaboration with the ARIC investigators.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	US /community
Risk factor/s assessed	Potential confounding variables measured	
CKD (creatinine clearance < 60 mL/min) and anaemia (WHO definition)	Age, gender, race, education, prevalent CHF, diabetes, SBP, DBP, HDL, LDL, carotid intima media thickness, current smoking.	
Population characteristics (including size)		
The ARIC study assessed a community-based middle-aged population aged 45–64 years (N=15,792). For the present study, participants were excluded if they had a self-reported history of stroke at baseline or if they had missing data on renal function, anaemia or other covariates of interest (final N=13,716). Mean age 54.1 years; 44.7% male; 24.8% African American.		

Length of follow-up	Outcomes measured
9 years	Stroke (defined as hospitalised fatal or non-fatal definite or probable stroke – evidence of rapid or sudden onset of neurologic symptoms consistent with stroke lasting for > 24 hours or leading to death, in the absence of evidence for a non-stroke cause). Strokes were identified by ARIC personnel making annual telephone calls to study participants and by conducting morbidity and mortality surveillance in local hospitals.

Method of analysis
Looked for significant interaction between CKD and anaemia in relation to stroke risk and when this was found, ran separate Cox models for the anaemic and non-anaemic subgroups in order to assess the multivariable adjusted association between creatinine clearance and stroke within each anaemia subgroup.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Fair Description: Data taken from a large prospective cohort study; analysis includes 87% of the 15,792 participants included at baseline; no details provided on how many declined to participate or loss to follow-up; not stated if outcome assessment blind to CKD/anaemia status; 9 years follow-up.
RESULTS

Population	With risk factor		Without risk factor	
Available	CKD NR/anaemia 1358		No CKD NR/no anaemia 12,782	
Analysed	CKD 2090/anaemia 1262		No CKD 11,626/no anaemia 12,454	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Stroke (N=1262)	CKD + anaemia	No CKD + anaemia	HR 5.43 (2.04, 14.41)	*CKD is an independent risk factor for increased risk of stroke in subjects with anaemia* P < 0.01
Stroke (N=12,454)	CKD + no anaemia	No CKD + no anaemia	HR 1.41 (0.93, 2.14)	*CKD is <u>not</u> an independent risk factor for increased risk of stroke in subjects without anaemia* P=0.1
Ischaemic stroke (N=1262)	CKD + anaemia	No CKD + anaemia	HR 10.34 (1.00, 29.0)	*CKD is an independent risk factor for increased risk of ischaemic stroke in subjects with anaemia* P=0.03

Ischaemic stroke (N=12,454)	CKD + no anaemia	No CKD + no anaemia	NR	*CKD is <u>not</u> an independent risk factor for increased risk of ischaemic stroke in subjects without anaemia* P=NR
EXTERNAL VALIDITY				
Generalisability				
This study was conducted in middle-aged subjects with and without CKD and with and without anaemia. The results of this study are generalisable to a middle-aged population but possible not to a younger or older population.				
Applicability				
This study was conducted in four regions in the US. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors note that a significant interaction was seen between CKD and anaemia for stroke (P=0.01). The authors conclude that "among middle-aged community-based persons, the combination of CKD and anemia was associated with a substantial increase in stroke risk, independent of other known risk factors for stroke". Potential limitations of this study included: (i) unidentified confounding (eg, by inflammation); (ii) estimation of CKD may have led to misclassification, although this was likely to have led to an underestimation; (iii) failure to identify subclinical strokes, which may have led to misclassification of stroke, which is also likely to have resulted to an underestimation; and (iv) the inability to examine different stroke types due to the moderate number of stroke events.				

CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; NR, not reported; SBP, spontaneous bacterial peritonitis; US, United States of America; WHO, World Health Organization.

STUDY DETAILS: Cohort study		
Citation		
Astor et al (2006) Kidney function and anaemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. American heart Journal 151: 492–500.		
Affiliation/Source of funds		
Johns Hopkins University, Baltimore; University of North Carolina, Chapel Hill; Amgen Inc, Thousand Oaks; Tufts New England Medical Center, Boston; US. The ARIC Study was funded by the National Heart, Lung and Blood Institute. This study was funded by Amgen Inc, the American Heart Association Mid Atlantic Affiliate, the National Heart, Lung and Blood Institute and an American Heart Association Established Investigator Award.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	US /community
Risk factor/s assessed	Potential confounding variables measured	
GFR (various levels) and anaemia (< 12 g/dL in women and < 13.5 g/dL in men)	Serum creatinine, age, gender, race, prevalent CHF, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	

Population characteristics (including size)				
The ARIC study assessed a community-based middle-aged population aged 45–64 years (N=15,792). For the present study, participants were excluded if they had a self-reported history of stroke at baseline or if they had missing data on renal function, anaemia or other covariates of interest, or a GFR < 30 mL/min and race other than African-American or Caucasian (final N=14,971). Mean age 54.2 years; 45.1% male; 26.1% African American.				
Length of follow-up	Outcomes measured			
12 years	Mortality, CHD mortality and CHD events. A CHD event was defined as a definite or probable myocardial infarction, definite CHD death, or coronary revascularisation.			
Method of analysis				
The independent relationships of kidney function and anaemia with events were tested with multivariable Cox proportional hazards regression models. The interaction of anaemia with kidney function was tested by adding an interaction term to the models.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Data taken from a large prospective cohort study; analysis includes 95% of the 15,792 participants included at baseline; 65–67% of eligible participants in three centres and 46% in another centre completed the baseline examination; not stated if outcome assessment blind to GFR/anaemia status; 12 years follow-up.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR		NR	
Analysed	GFR < 90 mL/min 7832/anaemia 1392		GFR ≥ 90 mL/min 7139/no anaemia 13,579	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All-cause mortality				
All-cause mortality (N=1130)	GFR 75–89 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 1.11 (0.80, 1.55)	*A GFR of 75–89 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for all-cause mortality in subjects with anaemia* P ≥ 0.05
All-cause mortality (N=11,257)	GFR 75–89 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 0.93 (0.83, 1.05)	*A GFR of 75–89 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for all-cause mortality in subjects without anaemia* P ≥ 0.05
All-cause mortality (N=923)	GFR 60–74 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 1.62 (1.12, 2.35)	*A GFR of 60–74 mL/min/1.73 m^2 is an independent risk factor for all-cause mortality in subjects with anaemia* P<0.05

All-cause mortality (N=8389)	GFR 60–74 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.02 (0.87, 1.20)	*A GFR of 60–74 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for all-cause mortality in subjects without anaemia* P ≥ 0.05
All-cause mortality (N=793)	GFR 30–59 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 3.49 (2.38, 5.12)	*A GFR of 30–59 mL/min/1.73 m^2 is an independent risk factor for all-cause mortality in subjects with anaemia* P < 0.001
All-cause mortality (N=6757)	GFR 30–59 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.72 (1.34, 2.20)	*A GFR of 30–59 mL/min/1.73 m^2 is an independent risk factor for all-cause mortality in subjects without anaemia* P < 0.001
CHD mortality				
CHD mortality (N=1130)	GFR 75–89 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 1.26 (0.59, 2.69)	*A GFR of 75–89 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for CHD mortality in subjects with anaemia* P ≥ 0.05
CHD mortality (N=11,257)	GFR 75–89 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 0.99 (0.76, 1.31)	*A GFR of 75–89 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for CHD mortality in subjects without anaemia* P ≥ 0.05
CHD mortality (N=923)	GFR 60–74 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 2.78 (1.30, 5.97)	*A GFR of 60–74 mL/min/1.73 m^2 is an independent risk factor for CHD mortality in subjects with anaemia* P < 0.001
CHD mortality (N=8389)	GFR 60–74 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.36 (0.98, 1.89)	*A GFR of 60–74 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for CHD mortality in subjects without anaemia* P ≥ 0.05

CHD mortality (N=793)	GFR 30–59 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 4.38 (1.96, 9.79)	*A GFR of 30–59 mL/min/1.73 m^2 is an independent risk factor for CHD mortality in subjects with anaemia* P < 0.001
CHD mortality (N=6757)	GFR 30–59 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 2.67 (1.71, 4.17)	*A GFR of 30–59 mL/min/1.73 m^2 is an independent risk factor for CHD mortality in subjects without anaemia* P < 0.001
Recurrent CHD				
Recurrent CHD (N=NR)	GFR 75–89 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 2.47 (0.96, 6.40)	*A GFR of 75–89 mL/min/1.73 m^2 is not an independent risk factor for recurrent CHD in subjects with anaemia* P ≥ 0.05
Recurrent CHD (N=NR)	GFR 75–89 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.00 (0.76, 1.31)	*A GFR of 75–89 mL/min/1.73 m^2 is not an independent risk factor for recurrent CHD in subjects without anaemia* P ≥ 0.05
Recurrent CHD (N=NR)	GFR 60–74 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 4.01 (1.01, 15.90)	*A GFR of 60–74 mL/min/1.73 m^2 is an independent risk factor for recurrent CHD in subjects with anaemia* P < 0.05
Recurrent CHD (N=NR)	GFR 60–74 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.44 (1.05, 1.98)	*A GFR of 60–74 mL/min/1.73 m^2 is an independent risk factor for recurrent CHD in subjects without anaemia* P < 0.05
Recurrent CHD (N=NR)	GFR 30–59 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 8.01 (1.86, 34.41)	*A GFR of 30–59 mL/min/1.73 m^2 is an independent risk factor for recurrent CHD in subjects with anaemia* P < 0.01

Recurrent CHD (N=NR)	GFR 30–59 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.30 (0.78, 2.18)	*A GFR of 30–59 mL/min/1.73 m^2 is not an independent risk factor for recurrent CHD in subjects without anaemia* P ≥ 0.05
De novo CHD				
De novo CHD (N=NR)	GFR 75–89 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 1.20 (0.77, 1.87)	*A GFR of 75–89 mL/min/1.73 m^2 is not an independent risk factor for de novo CHD in subjects with anaemia* P ≥ 0.05
De novo CHD (N=NR)	GFR 75–89 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.05 (0.92, 1.20)	*A GFR of 75–89 mL/min/1.73 m^2 is not an independent risk factor for de novo CHD in subjects without anaemia* P ≥ 0.05
De novo CHD (N=NR)	GFR 60–74 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 1.48 (0.87, 2.51)	*A GFR of 60–74 mL/min/1.73 m^2 is not an independent risk factor for de novo CHD in subjects with anaemia* P ≥ 0.05
De novo CHD (N=NR)	GFR 60–74 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.04 (0.87, 1.25)	*A GFR of 60–74 mL/min/1.73 m^2 is not an independent risk factor for de novo CHD in subjects without anaemia* P ≥ 0.05
De novo CHD (N=NR)	GFR 30–59 mL/min/1.73 m^2 + anaemia	GFR ≤ 90 mL/min/1.73 m^2 + anaemia	HR 1.58 (0.83, 3.02)	*A GFR of 30–59 mL/min/1.73 m^2 is not an independent risk factor for de novo CHD in subjects with anaemia* P ≥ 0.05

De novo CHD (N=NR)	GFR 30–59 mL/min/1.73 m^2 + no anaemia	GFR ≤ 90 mL/min/1.73 m^2 + no anaemia	HR 1.26 (0.91, 1.75)	*A GFR of 30–59 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for de novo CHD in subjects without anaemia* P ≥ 0.05
EXTERNAL VALIDITY				
Generalisability				
This study was conducted in middle-aged subjects with and without low GFR and with and without anaemia. The results of this study are generalisable to a middle-aged population but possible not to a younger or older population.				
Applicability				
This study was conducted in four regions in the US. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that "the combination of moderately decreased kidney function [GFR 30–59 mL/min/1.73 m^2] is associated with an increased risk of CHD events and mortality". Although in some cases there was no significant difference in either the anaemia or non-anaemia groups, the authors note that "the excess risk of each end point associated with decreased kidney function … was > 2-fold greater among individuals with anaemia than among individuals without anaemia". Limitations of the study included the possibility of residual confounding and possible misclassification.				

BMI, body mass index; CHD, chronic heart disease; CI, confidence interval; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; NR, not reported; min, minute; mL, millilitre; SBP, spontaneous bacterial peritonitis; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Avram et al (2003) Hemoglobin predicts long-term survival in dialysis patients: a 15-year single-center longitudinal study and a correlation trend between prealbumin and hemoglobin. Kidney International 64 (Supplement 87): S6-S11.		
Affiliation/Source of funds		
Long Island College Hospital, Brooklyn, US. Supported in part by grants from the Kidney and Urology Foundation of America and the Nephrology Foundation of Brooklyn.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	US/hospital (single-centre)
Risk factor/s assessed	Potential confounding variables measured	
Haemoglobin (and others)	Age, gender, race, diabetes (continuous variable only) and months on dialysis at enrolment.	
Population characteristics (including size)		
Patients on haemodialysis (HD) or peritoneal dialysis (PD). Mean age 60 (HD) and 54 (PD); female 55% (HD) and 53% (PD); African-American 60% (HD) and 59% (PD). N=529 (HD) and 326 (PD)		
Length of follow-up	Outcomes measured	

Mean 3.99 years (maximum 16.04 years)		Mortality		
Method of analysis				
Multivariate Cox regression was used to determine independent predictors of survival. Logistic regression analysis was used to investigate the association between risk of death and explanatory variables.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective, single-centre, hospital-based cohort study; does not state if any patients refused participation; all patients followed up; no adjustment for co-morbidities, other than for diabetes in the continuous analysis; follow-up up to 16 years (mean 4 years).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR		NR	
Analysed	NR		NR	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (N=529) *Haemodialysis (all patients)*	Hb < 12 g/dL	Hb ≥ 12 g/dL	RR 2.13	*Hb < 12 g/dL is an independent risk factor for increased mortality in haemodialysis patients* P=0.008
Mortality (N=312) *Haemodialysis (non-diabetic patients)*	Hb < 12 g/dL	Hb ≥ 12 g/dL	RR 4.53	*Hb < 12 g/dL is an independent risk factor for increased mortality in haemodialysis patients without diabetes* P=0.003
Mortality (N=217) *Haemodialysis (diabetic patients)*	Hb < 12 g/dL	Hb ≥ 12 g/dL	RR 0.74	*Hb < 12 g/dL is <u>not</u> an independent risk factor for increased mortality in haemodialysis patients with diabetes* P=0.39
Mortality (N=326) *Peritoneal dialysis (all patients)*	Hb < 12 g/dL	Hb ≥ 12 g/dL	RR 1.85	*Hb < 12 g/dL <u>may</u> be an independent risk factor for increased mortality in peritoneal dialysis patients* P=0.06
Mortality (N=326) *Peritoneal dialysis (non-diabetic patients)*	Hb < 12 g/dL	Hb ≥ 12 g/dL	RR 2.02	*Hb < 12 g/dL <u>may</u> be an independent risk factor for increased mortality in peritoneal dialysis patients* P=0.07

Mortality (N=326) *Peritoneal dialysis (diabetic patients)*	Hb < 12 g/dL	Hb ≥ 12 g/dL	RR 1.15	*Hb < 12 g/dL is <u>not</u> an independent risk factor for increased mortality in peritoneal dialysis patients* P=0.81
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value
Mortality (N=529) *Haemodialysis*	1 g/dL increment in Hb		OR 0.83	*A 1 g/dL increment in Hb results in a 17% reduction in risk of mortality in patients on haemodialysis* P=0.002
Mortality (N=326) *Peritoneal dialysis*	1 g/dL increment in Hb		OR 0.85	*A 1 g/dL increment in Hb results in a 15% reduction in risk of mortality in patients on peritoneal dialysis* P=0.02
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to patients in haemodialysis or peritoneal dialysis.				
Applicability				
This study was conducted at a single centre in the US with a 60% African American population. The results of this study may be applicable to the Australian setting.				
Comments				
The authors conclude that enrolment Hb is a predictor of long-term survival in HD and PD patients. As noted in the Volkova review, diabetes was a possible effect modifier and wasn't adjusted for in the categorical analyses. Diabetes was adjusted for in the continuous Hb level analysis which showed increasing Hb to be significantly associated with a reduction in mortality risk in both haemodialysis and peritoneal dialysis patients. The study did not adjust for comorbidities so it is possible that there is residual confounding.				

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; HD, haemodialysis; NR, not reported; OR, odds ratio; PD, post-dialysis; RR, relative risk; US, United States of America.

STUDY DETAILS: Cohort study
Citation
Finkelstein et al (2009) Health-related quality of life and hemoglobin levels in chronic kidney disease patients. Clin J Am Soc Nephrol 4: 33–38.
Affiliation/Source of funds
Hospital of St Raphael, Yale University, New Haven, US; Baxter Healthcare Corporation, Deerfield, US; Humber Regional Hospital, Toronto, Canada; McGill University, Montreal, Canada; Queen Elizabeth II Hospital, Halifax, Canada; Astellas Pharma US, Deerfield, US. Funding not stated.

Study design	Level of evidence	Location/setting
Prospective cohort study (cross-sectional analysis)	Level II	US and Canada/hospital

Risk factor/s assessed	Potential confounding variables measured
Hb levels (measured within 60 days of QoL assessment)	Age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)

Population characteristics (including size)
Patients with CKD, defined as an eGFR < 60 mL/min/1.73m2 (MDRD) stages 3–5 not on dialysis and aged 18 or older; mean age 65.6, male 58%, Caucasian 73%. N=1186

Length of follow-up	Outcomes measured
-	Quality of life (SF-36 and KDQoL); showing SF-36 only

Method of analysis
ANOVA used to determine if the scores from various domains were related to Hb and other factors.

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Fair Description: Cross-sectional analysis of data from a prospective cohort study (CRIOS); 2295 patients enrolled from 7 centres in US and Canada; 1186 completed the QoL questionnaires; only data collected within 60 days of QoL assessment included in analysis (numbers not provided); subjects who completed the QoL assessment were similar to those who did not with the exception of age and % men; analysis adjusted for a number of confounders including ESA use; subjective outcome, unclear if subjects aware of Hb status when completing QoL assessment.

RESULTS				
Population	With risk factor		Without risk factor	
Available	1186			
Analysed	Unknown			
Outcome (categorical)	Risk factor definition	No risk factor definition	QoL score	Significance P-value
SF-36 – mental component summary (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)		49.7, 50.5, 50.0, 49.5	*Increasing Hb level is <u>not</u> an independent risk factor for change in mental component summary score* P=0.82
SF-36 – physical component summary (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)		37.4, 39.9, 38.5, 41.0	*Increasing Hb level is an independent risk factor for an increase in physical component summary score* P=0.008

SF-36 – physical functioning (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	51.2, 56.9, 53.1, 60.7	*Increasing Hb level is an independent risk factor for an increase in physical functioning score* P=0.003
SF-36 – role-physical (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	40.8, 51.7, 47.1, 56.9	*Increasing Hb level is an independent risk factor for an increase in role-physical score* P=0.002
SF-36 – pain (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	67.4, 71.4, 63.7, 70.8	*Increasing Hb level is an independent risk factor for an increase in pain score* P=0.015
SF-36 – general health (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	44.9, 47.0, 45.9, 50.4	*Increasing Hb level is an independent risk factor for an increase in general health score* P=0.049
SF-36 – emotional wellbeing (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	73.0, 76.3, 73.9, 73.2	*Increasing Hb level is <u>not</u> an independent risk factor for change in emotional wellbeing score* P=0.29
SF-36 – role-emotional (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	68.5, 73.4, 68.2, 75.6	*Increasing Hb level is <u>not</u> an independent risk factor for change in role emotional score* P=0.18
SF-36 – social function (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	71.7, 76.9, 72.8, 76.2	*Increasing Hb level is <u>not</u> an independent risk factor for change in social function* P=0.15
SF-36 – energy-fatigue (N=NR)	Hb categories (< 11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥ 13 g/dL)	43.4, 48.8, 49.0, 50.1	*Increasing Hb level is an independent risk factor for an increase in energy/fatigue score* P=0.02
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population with CKD who are not yet undergoing dialysis.			
Applicability			
This study was conducted in the US and Canada. The results of this study are likely to be applicable to the Australian setting.			

Comments
The authors conclude that "higher Hgb levels are associated with improved QoL domains of the KDQoL questionnaire [which includes the SF-36]." Most dramatic changes occurred between Hb levels <11 and 11–12 g/dL. Analyses were adjusted for EPO therapy, and the interaction between Hb and EPO was tested and shown to be non significant for all domains. Limitations noted by the authors include the exclusion of subjects who did not have a Hb measurement within 60 days of the QoL assessment (~50% of population) and whether the findings can be generalised outside of the included centres.

ANOVA, analysis of variance; CI, confidence interval, CKD, chronic kidney disease; dL, decilitre; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; g, grams; Hb, haemoglobin; KDQoL, Kidney Disease Quality of Life; MDRD, Modification of Diet in Renal Disease; min, minutes; mL, millilitre; NR, not reported; QoL, quality of life; SF-36, Short Form (36) Health Survey; USA, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Fort et al (2010) Mortality in incident haemodialysis patients: time-dependent haemoglobin levels and erythropoiesis-stimulating agent dose are independent predictive factors in the ANSWER study. Nephrol Dial Transplant 25: 2702–2710.		
Affiliation/Source of funds		
Hospital Vall d'Hebron, Barcelona; Hospital Consorci Sanitara de Terrassa, barcelone; Hospital Universitario Puerto de Hierro, Madrid; Hospital Infanta Leonor, Madrid; Amgen SA, Barcelona; Hospital Universitario Reina Sofia, Cordoba; Spain. Supported in part by the Spanish Society of Nephrology and in part by a grant from Amgen SA, Spain.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	Spain/hospital
Risk factor/s assessed	Potential confounding variables measured	
Hb level (and ESA dose)	Age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	
Population characteristics (including size)		
Patients starting haemodialysis, who had received haemodialysis for ≤ 30 days, aged ≥ 18 years. Mean age 65.2 years; male 63%, European 98%. N=2310		
Length of follow-up	Outcomes measured	
2 years (mean 1.5 years)	All-cause mortality	
Method of analysis		
Multivariate time-dependent Cox regression models were constructed to assess the association of Hb with all-cause mortality after adjusting for ESA dose, iron status and socio-demographic, clinical, laboratory and health care variables. Additional models were also constructed using baseline Hb and 6-month Hb.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Prospective hospital-based cohort study; 62.5% (147/235) of dialysis facilities agreed to participate; baseline characteristics are reported for 2341 patients which it is reported makes up ~58% of all incident dialysis patients during the study period; 2310 were ultimately included in the study (no reason for the reduced number is given); follow up was up to 2 years (mean 1.5 years).		
RESULTS		

Population	With risk factor		Without risk factor	
Available	2341			
Analysed	2310			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Time-dependent haemoglobin				
All-cause mortality (N=NR)	Time-dependent Hb ≤ 10 g/dL	Time-dependent Hb 11.1–12.0 g/dL	HR 1.36 (1.01, 1.86)	*A time-dependent Hb level of ≤ 10 g/dL is an independent predictor of all-cause mortality compared with a time-dependent Hb level of 11.1–12.0 g/dL* P=0.048
All-cause mortality (N=NR)	Time-dependent Hb 10.1–11.0 g/dL	Time-dependent Hb 11.1–12.0 g/dL	HR 1.03 (0.75, 1.42)	*A time-dependent Hb level of 10.1–11.0 g/dL is not an independent predictor of all-cause mortality compared with a time-dependent Hb level of 11.1–12.0 g/dL* P=0.83
All-cause mortality (N=NR)	Time-dependent Hb 12.1–13.0 g/dL	Time-dependent Hb 11.1–12.0 g/dL	HR 0.93 (0.68, 1.26)	*A time-dependent Hb level of 12.1–13.0 g/dL is not an independent predictor of all-cause mortality compared with a time-dependent Hb level of 11.1–12.0 g/dL* P=0.63
All-cause mortality (N=NR)	Time-dependent Hb ≥ 13.0 g/dL	Time-dependent Hb 11.1–12.0 g/dL	HR 0.69 (0.49, 0.97)	*A time-dependent Hb level of ≥13.0 g/dL is an independent predictor of a reduced risk of all-cause mortality compared with a time-dependent Hb level of 11.1–12.0 g/dL* P=0.03
Baseline haemoglobin				
All-cause mortality (N=NR)	Baseline Hb ≤ 10 g/dL	Baseline Hb 11.1–12.0 g/dL	HR 1.23 (0.92, 1.64)	*A baseline Hb level of ≤ 10 g/dL is not an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1–12.0 g/dL* P=NR

All-cause mortality (N=NR)	Baseline Hb 10.1–11.0 g/dL	Baseline Hb 11.1–12.0 g/dL	HR 1.11 (0.81, 1.53)	*A baseline Hb level of 10.1–11.0 g/dL is <u>not</u> an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1–12.0 g/dL* P=NR
All-cause mortality (N=NR)	Baseline Hb 12.1–13.0 g/dL	Baseline Hb 11.1–12.0 g/dL	HR 1.01 (0.68, 1.52)	*A baseline Hb level of 12.1–13.0 g/dL is <u>not</u> an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1–12.0 g/dL* P=NR
All-cause mortality (N=NR)	Baseline Hb ≥ 13.0 g/dL	Baseline Hb 11.1–12.0 g/dL	HR 0.77 (0.44, 1.36)	*A baseline Hb level of ≥13.0 g/dL is <u>not</u> an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1–12.0 g/dL* P=NR
6-month haemoglobin				
All-cause mortality (N=897)	6-month Hb ≤ 10 g/dL	6-month Hb 11.1–12.0 g/dL	HR 2.32 (1.73, 3.12)	*A 6-month Hb level of ≤ 10 g/dL is an independent predictor of all-cause mortality compared with a 6-month Hb level of 11.1–12.0 g/dL* P=NR
All-cause mortality (N=902)	6-month Hb 10.1–11.0 g/dL	6-month Hb 11.1–12.0 g/dL	HR 1.46 (1.06, 2.01)	*A 6-month Hb level of 10.1–11.0 g/dL is an independent predictor of all-cause mortality compared with a 6-month Hb level of 11.1–12.0 g/dL* P=NR
All-cause mortality (N=1063)	6-month Hb 12.1–13.0 g/dL	6-month Hb 11.1–12.0 g/dL	HR 0.94 (0.69, 1.29)	*A 6-month Hb level of 12.1–13.0 g/dL is <u>not</u> an independent predictor of all-cause mortality compared with a 6-month Hb level of 11.1–12.0 g/dL* P=NR

All-cause mortality (N=1086)	6-month Hb ≥ 13.0 g/dL	6-month Hb 11.1–12.0 g/dL	HR 0.71 (0.51, 0.99)	*A 6-month Hb level of ≥13.0 g/dL is an independent predictor of a reduced risk of all-cause mortality compared with a 6-month Hb level of 11.1–12.0 g/dL* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to an adult population starting haemodialysis.				
Applicability				
This study was conducted in Spain. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that "higher haemoglobin levels are associated with lower mortality in Spanish incident haemodialysis patients, regardless of ESA dose, iron deficiency, comorbidity, vascular access or malnutrition". The authors performed a number of sensitivity analyses which showed similar results with the following exceptions: (i) when patients who died within 6 months were excluded (177), the Hb ≤ 10 g/dL analysis failed to reach statistical significance; and (ii) when patients with or without previous CV history were assessed, there was no association between Hb and mortality in patients without previous CV history but there was in those with previous CV history. The authors note a number of potential limitations of the study including the lack of measurement at 4–8 weeks following an ESA dose change which prevented assessment of whether administered ESA doses were effective or not; measures of intra-patient Hb variability were not included; and possibility of residual confounding.				

BMI, body mass index; CI, confidence interval; dL, decilitre; ESA, erythropoiesis stimulating agent; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported

STUDY DETAILS: Cohort study		
Citation		
Leeder et al (2005) Low hemoglobin, chronic kidney disease, and risk for coronary heart disease-related deaths: the Blue Mountains Eye Study. J Am Soc Nephrol 17: 279–284.		
Affiliation/Source of funds		
University of Sydney, Sydney; University of Newcastle, Newcastle; Australia. Supported by the Australian National Health and Medical Research Council.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	Australia/community
Risk factor/s assessed	Potential confounding variables measured	
Baseline Hb (quintiles) and CKD(GFR < 60ml/min/1.73 m^2)	Age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	
Population characteristics (including size)		
Residents of two postcode areas in the Blue Mountains born before January 1, 1943 (N=3074). Only subjects with CKD based on three estimation methods (N=1639, 1427 and 1258) or low serum creatinine (N=294) are included in this review.		

Length of follow-up	Outcomes measured
Mean 8.2 years for overall study population	CHD-related death (death confirmed by cross-matching demographic information with Australian National Death Index [NDI] data). Cause of death collected from death certificates and defined using ICD-9 and ICD-10 codes.

Method of analysis
Cox regression models were used to assess the association between baseline Hb and CHD mortality.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good Description: Prospective, community-based cohort study; 580 (15.9%) excluded due to missing or incomplete data; those excluded were similar to the included population except for having more pre-existing CHD and higher rates of CHD deaths; adjusted for a number of potential confounding factors; mean 8.2 years follow-up.
RESULTS

Population	With risk factor		Without risk factor	
Available	3654			
Analysed	3074 (population with CKD varied from 294 to 1639 depending on method used to measure CKD)			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
CHD-related death (N=1639) *CKD by Cockcroft-Gault method*	Lowest Hb quintile (mean 13.1 g/dL)	Other Hb quintiles (mean 15.2 g/dL)	HR 1.49 (1.08, 2.06)	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR
CHD-related death (N=1427) *CKD by abbreviated MDRD*	Lowest Hb quintile (not defined)	Other Hb quintiles (not defined)	HR 1.36 (0.95, 1.94)	*The lowest quintile of Hb is <u>not</u> an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR
CHD-related death (N=1258) *CKD by Bjornsson*	Lowest Hb quintile (not defined)	Other Hb quintiles (not defined)	HR 1.57 (1.12, 2.19)	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR

CHD-related death (N=294) *CKD by serum creatinine*	Lowest Hb quintile (not defined)	Other Hb quintiles (not defined)	HR 1.80 (1.02, 3.18)	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR
CHD-related death (N=NR) *CKD by Cockcroft-Gault method (lowest quintile GFR)*	Lowest Hb quintile (mean 13.1 g/dL)	Other Hb quintiles (mean 15.2 g/dL)	HR 2.07 (1.33, 3.22)	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR
CHD-related death (N=NR) *CKD in <u>women</u> by Cockcroft-Gault method (lowest quintile GFR)*	Lowest Hb quintile (mean 13.1 g/dL)	Other Hb quintiles (mean 15.2 g/dL)	HR 1.82 (0.88, 3.78)	*The lowest quintile of Hb is <u>not</u> an independent risk factor for CHD-related mortality compared with other Hb quintiles in women with the lowest quintile GFR.* P=NR
CHD-related death (N=NR) *CKD in <u>men</u> by Cockcroft-Gault method (lowest quintile GFR)*	Lowest Hb quintile (mean 13.1 g/dL)	Other Hb quintiles (mean 15.2 g/dL)	HR 2.32 (1.29, 4.17)	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles in women with the lowest quintile GFR.* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with CKD based on definitions by eGFR or serum creatinine.				
Applicability				
This study was conducted in Australia. The results of this study are directly applicable to the Australian setting.				
Comments				
The authors conclude that "low hemoglobin, even within the normal range, together with CKD increased the risk for CHD-related deaths". The authors note that they performed sensitivity analyses using different GFR cut-offs and obtained essentially the same results. They note that they confirm and extend the findings of the ARIC study (Jurkovitz 2003). Potential limitations of the study are: (i) potential misclassification of CKD by estimation of GFR, although they used different methods to minimise this; (ii) using serum fibrinogen to control for systemic inflammation, as this may not have been adequate; and (iii) exclusion of 15.9% of the initial sample as this may have introduced selection bias, although excluded subjects were mostly similar to included subjects except for more pre-existing CHD and more CHD-related deaths.				

BMI, body mass index; BP, blood pressure; CI, confidence interval, CHD, chronic heart disease; CKD, chronic kidney disease; dL, decilitre; g, grams; Hb, haemoglobin; HR, hazard ratio; ICD, International Classification of Diseases; NR, not reported

STUDY DETAILS: Cohort study			
Citation			
Merkus et al (1997) Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. American journal of Kidney Diseases 29(4): 584–592.			
Affiliation/Source of funds			
Academic Medical Center, Amsterdam, The Netherlands. Supported by a grant from the Dutch Kidney Foundation.			
Study design	Level of evidence	Location/setting	
Cross-sectional analysis of prospectively collected data	Level II	The Netherlands/hospital	
Risk factor/s assessed	Potential confounding variables measured		
Various (including Hb)	Variables shown to be P≤ 0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.		
Population characteristics (including size)			
Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995; mean age ~56 years, male ~ 61%. N=226			
Length of follow-up	Outcomes measured		
-	QoL (SF-36)		
Method of analysis			
Used multiple linear regression with a stepwise forward selection strategy.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Cross-sectional study; of 250 available for the study, 226 (90.4%) completes the SF-36; those who did not complete it either didn't speak Dutch well enough and/or could not read and fill out the questionnaire themselves; those who did not complete the SF-36 were more likely to be male, and have a lower Hb; analysis adjusted for a number of confounders based on univariate analysis and stepwise selection; unclear if patients aware of Hb status (subjective outcome).			
RESULTS			
Population	With risk factor	Without risk factor	
Available	250		
Analysed	226		
Outcome (continuous)	Continuous measure	Regression coefficient (partial explained variance)	Significance P-value
SF-36 – physical functioning (N=226)	Hb	NR	*Hb is <u>not</u> significantly associated with physical functioning score* P=NR

SF-36 – social functioning (N=226)	Hb	0.23 (6.1%)	*Hb is significantly associated with social functioning score* P=NR
SF-36 – role physical (N=226)	Hb	NR	*Hb is <u>not</u> significantly associated with role physical score* P=NR
SF-36 – role emotional (N=226)	Hb	0.13 (1.7%)	*Hb is significantly associated with role emotional score* P=NR
SF-36 – mental health (N=226)	Hb	NR	*Hb is <u>not</u> significantly associated with mental health score* P=NR
SF-36 – vitality (N=226)	Hb	0.15 (2.5%)	*Hb is significantly associated with vitality score* P=NR
SF-36 – bodily pain (N=226)	Hb	NR	*Hb is <u>not</u> significantly associated with bodily pain score* P=NR
SF-36 – general health perceptions (N=226)	Hb	NR	*Hb is <u>not</u> significantly associated with general health perceptions score* P=NR
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population initiating haemodialysis or peritoneal dialysis.			
Applicability			
This study was conducted in the Netherlands. The results of this study may be generalisable to the Australian setting.			
Comments			
The authors conclude that multivariate analysis showed that a higher number of comorbid conditions, a lower haemoglobin level, and a lower residual renal function (rGFR) were the most important independent explanatory factors for poorer quality of life." However, the authors note that the total explained variation by all identified characteristics was small.			

CI, confidence interval; GFR, glomerular filtration rate; Hb, haemoglobin; nPCR, normalised protein catabolic rate; nPNA, normalised protein nitrogen appearance; NR, not reported; QoL, quality of life; rGFR, residual glomerular filtration rate; SF-36, Short Form (36) Health Survey.

STUDY DETAILS: Cohort study			
Citation			
Mollaoglu (2004) Depression and health-related quality of life in hemodialysis patients. Dialysis and Transplantation 33(9): 544–579.			
Affiliation/Source of funds			
University of Cumhuriyet, Sivas, Turkey. Funding not stated.			
Study design	Level of evidence	Location/setting	
Cross-sectional analysis of prospectively collected data	Level II	Turkey/Hospital	
Risk factor/s assessed	Potential confounding variables measured		
Depression (includes Hb)	Age, sex, serum albumin and BDI.		
Population characteristics (including size)			
Population taken from a 2-year longitudinal study of quality of life; prevalent haemodialysis patients; mean age 51.0, male 53.6%. N=140			
Length of follow-up	Outcomes measured		
-	QoL (SF-36)		
Method of analysis			
Multivariate analysis using multiple linear regression analysis.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: Cross-sectional study; 140/150 eligible patients completed the SF-36 and BDI (no details of excluded subjects provided); only adjusted for a small number of potential confounders; subjective outcome – unclear if subjects aware of Hb status.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	150		
Analysed	140		
Outcome (continuous)	Continuous measure	Regression coefficient	Significance P-value
SF-36 – mental component score (N=140)	Hb	0.121	*Hb is <u>not</u> significantly associated with mental component score* P ≥ 0.05
SF-36 – physical component score (N=140)	Hb	0.0329	*Hb is <u>not</u> significantly associated with physical component score* P ≥ 0.05
EXTERNAL VALIDITY			
Generalisability			

The results of this study are generalisable to an adult population already on haemodialysis.
Applicability
This study was conducted in Turkey. The results of this study may be applicable to the Australian setting.
Comments
No specific comments regarding the association between Hb and QoL have been noted. Global BDI was an independent predictor of both MCS and PCS in this population.

BDI; Beck Depression Inventory; CI, confidence interval, Hb, haemoglobin.; QoL, quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36, Short Form (36) Health Survey.

STUDY DETAILS: Cohort study		
Citation		
Perlman et al (2005) Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the renal research institute–CKD study. American journal of Kidney Diseases 45(4): 659–666.		
Affiliation/Source of funds		
University of Michigan; University Renal Research and Education Association, Ann Arbor; Yale University, New Haven; University of North Carolina, Chapel Hill; Albany Medical Center, Albany; Mount Sinai Medical School, New York; Amgen Inc, Thousand Oaks; US. Supported in part by a grant from the Renal Research Institute, New York and Amgen Inc.		
Study design	Level of evidence	Location/setting
Cross-sectional study	Level II	US/hospital
Risk factor/s assessed	Potential confounding variables measured	
Various (including Hb)	Age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.	
Population characteristics (including size)		
CKD defined as a GFR ≤ 50 mL/min/1.73 m^2 (MDRD); overall cohort mean age 60.7 years, male 56%, Caucasian 75%; SF-36 population mean age 60.2, male 58%, Caucasian 77%; 487 with Hb measurement. Differences between those completing and not completing the SF-36 included % Caucasian (77% vs 66%), diabetes (35% vs 45%) and college education (66% vs 45%). N=222 (all variables available), 487 (Hb available).		
Length of follow-up	Outcomes measured	
-	QoL (SF-36)	
Method of analysis		
Used multiple linear regression.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Cross-sectional study; overall cohort (N=634) mean age 60.7 years, male 56%, Caucasian 75%; SF-36 population (N=505) mean age 60.2, male 58%, Caucasian 77%; 487 with Hb measurement. Differences between those completing and not completing the SF-36 included % Caucasian (77% vs 66%), diabetes (35% vs 45%) and college education (66% vs 45%); authors note they did not detect bias; analysis adjusted for a number of confounders; subjective outcome (unclear if Hb status known).		
RESULTS		
Population	With risk factor	Without risk factor

Available	634		
Analysed	222 (all variables available), 487 (Hb available).		
Outcome (continuous)	Continuous measure	Parameter estimate	Significance P-value
SF-36 – physical function (N=NR)	Hb	2.3	*Hb level is significantly associated with physical function score* P < 0.05
SF-36 – physical role (N=NR)	Hb	4.8	*Hb level is significantly associated with physical role score* P < 0.05
SF-36 – pain (N=NR)	Hb	2.3	*Hb level is not significantly associated with pain score* P = NR
SF-36 – general health (N=NR)	Hb	2.0	*Hb level is significantly associated with general health score* P < 0.05
SF-36 – mental health (N=NR)	Hb	1.6	*Hb level is significantly associated with mental health score* P < 0.05
SF-36 – emotional role (N=NR)	Hb	4.0	*Hb level is significantly associated with emotional role score* P < 0.05
SF-36 – social function (N=NR)	Hb	4.1	*Hb level is significantly associated with social function score* P < 0.01
SF-36 – vitality (N=NR)	Hb	2.3	*Hb level is significantly associated with vitality score* P < 0.05
SF-36 – physical component score (N=NR)	Hb	1.1	*Hb level is significantly associated with physical component score* P < 0.05
SF-36 – mental component score (N=NR)	Hb	1.1	*Hb level is significantly associated with mental component score* P < 0.05
EXTERNAL VALIDITY			
Generalisability			

The results of this study are generalisable to a population with CKD.
Applicability
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.
Comments
The authors note that Hb level "correlated positively with each individual and component scale and was a statistically significant predictor for 7 of 8 individual scales (all except Pain), the MCS, and the PCS." The authors note that a limitation of the study is the large amount of missing data, as well as the lack of centralised laboratory testing.

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval, CHF, chronic heart failure; CKD, chronic kidney disease; Hb, haemoglobin; HTN, hypertension; GFR, gromerular filtration rate; MCS, Mental Component Summary; MDRD, Modification of Diet in Renal Disease; mL, millilitre; NR, not reported; PCS, Physical Component Summary; QoL, quality of life; SF-36, Short Form (36) Health Survey; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Plantinga et al (2007) Relation between level or change of hemoglobin and generic and disease-specific quality of life measures in hemodialysis. Qual Life Res 16: 755–765.		
Affiliation/Source of funds		
Johns Hospkins Medical Institutions, Baltimore; Johns Hopkins Bloomberg School of Public Health, Baltimore; Nephrology Center of Maryland, Baltimore; University of Florida, Gainesville; Tufts-New England Medical Center, Boston; US. Supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, the AHRZ and the National Heart Lung and Blood Institute.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	US/hospital
Risk factor/s assessed	Potential confounding variables measured	
Hb levels	Those that had a significant association with both haemoglobin at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.	
Population characteristics (including size)		
Patients initiating haemodialysis during 10/95 to 6/98; mean age ~59 years; ~54% male; ~62% Caucasian.		
Length of follow-up	Outcomes measured	
12 months	QoL (generic: SF-36 and disease-specific: designed for study). Only SF-36 considered here.	
Method of analysis		
Multivariable linear regression models were used.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Prospective cohort study with both cross-sectional and longitudinal analyses; 767 patients available; 313 did not have 1-year QoL and 16 did not have 6-month Hb; authors state that those missing from analysis were similar to those included; analyses adjusted for a few potential confounders, these chosen based on analyses or known association with QoL; subjective outcomes, unclear if measured without awareness of anaemia status.		

RESULTS				
Population	With risk factor		Without risk factor	
Available	767			
Analysed	169		269	
Outcome (categorical)	No risk factor definition	Risk factor definition	Risk estimate (95% CI)	Significance P-value
1-year SF-36 – physical component score (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 1.56 (0.16, 2.96)	*Hb ≥ 11 g/dL is an independent predictor of greater physical component score compared with Hb < 11 g/dL* P<0.05
1-year SF-36 – mental component score (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 2.49 (0.35, 4.62)	*Hb ≥ 11 g/dL is an independent predictor of greater mental component score compared with Hb < 11 g/dL* P<0.05
1-year SF-36 – physical functioning (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 5.02 (1.44, 8.60)	*Hb ≥ 11 g/dL is an independent predictor of greater physical functioning score compared with Hb < 11 g/dL* P<0.05
1-year SF-36 – role physical (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 6.07 (0.69, 11.5)	*Hb ≥ 11 g/dL is an independent predictor of greater role physical score compared with Hb < 11 g/dL* P<0.05
1-year SF-36 – general health (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 2.63 (-2.12, 7.38)	*Hb ≥ 11 g/dL is <u>not</u> an independent predictor of greater general health score compared with Hb < 11 g/dL* P=NR
1-year SF-36 – bodily pain (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 6.16 (2.37, 9.96)	*Hb ≥ 11 g/dL is an independent predictor of greater bodily pain score compared with Hb < 11 g/dL* P<0.05

1-year SF-36 – role emotional (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 9.99 (-0.64, 20.6)	*Hb ≥ 11 g/dL is <u>not</u> an independent predictor of greater role emotional score compared with Hb < 11 g/dL* P=NR
1-year SF-36 – mental health (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 5.12 (2.31, 7.93)	*Hb ≥ 11 g/dL is an independent predictor of greater mental health score compared with Hb < 11 g/dL* P<0.05
1-year SF-36 – social functioning (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 5.72 (0.33, 11.1)	*Hb ≥ 11 g/dL is an independent predictor of greater social functioning score compared with Hb < 11 g/dL* P<0.05
1-year SF-36 – vitality (N=438)	6 month Hb ≥ 11 g/dL	6 month Hb < 11 g/dL	MD 2.39 (-0.51, 5.29)	*Hb ≥ 11 g/dL is <u>not</u> an independent predictor of greater vitality score compared with Hb < 11 g/dL* P=NR
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value
Cross-sectional analysis				
1-year SF-36 – physical component score (N=438)	1 g/dL increment 6-month Hb		MD 0.92 (0.22, 1.62)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in physical component score* *P*<0.05
1-year SF-36 – mental component score (N=438)	1 g/dL increment 6-month Hb		MD 1.42 (0.72, 2.12)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in mental component score* *P*<0.05

1-year SF-36 – physical functioning (N=438)	1 g/dL increment 6-month Hb	MD 2.61 (0.51, 4.71)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in physical functioning score* *P*<0.05
1-year SF-36 – role physical (N=438)	1 g/dL increment 6-month Hb	MD 2.81 (0.37, 5.26)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in role physical score* *P*<0.05
1-year SF-36 – general health (N=438)	1 g/dL increment 6-month Hb	MD 5.28 (2.38, 8.18)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in general health score* *P*<0.05
1-year SF-36 – bodily pain (N=438)	1 g/dL increment 6-month Hb	MD 3.12 (0.94, 5.29)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in bodily pain score* *P*<0.05
1-year SF-36 – role emotional (N=438)	1 g/dL increment 6-month Hb	MD 3.75 (2.28, 5.22)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in role emotional score* *P*<0.05
1-year SF-36 – mental health (N=438)	1 g/dL increment 6-month Hb	MD 1.90 (0.27, 3.52)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in mental health score* *P*<0.05
1-year SF-36 – social functioning (N=438)	1 g/dL increment 6-month Hb	MD 2.60 (1.35, 3.85)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in social functioning score* *P*<0.05
1-year SF-36 – vitality (N=438)	1 g/dL increment 6-month Hb	MD 2.44 (1.10, 3.78)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in vitality score* *P*<0.05

Longitudinal analysis			
Baseline to 1-year change in SF-36 – physical component score (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 0.64 (0.16, 1.11)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in physical component score* *P*<0.05
Baseline to 1-year change in change in 1-year SF-36 – mental component score (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 0.80 (0.27, 1.33)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in mental component score* *P*<0.05
Baseline to 1-year change in change in SF-36 – physical functioning (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 1.51 (0.39, 2.62)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in physical functioning score* *P*<0.05
Baseline to 1-year change in change in SF-36 – role physical (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 2.72 (1.03, 4.40)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in role physical score* *P*<0.05
Baseline to 1-year change in change in SF-36 – general health (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 1.33 (0.41, 2.26)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in general health score* *P*<0.05
Baseline to 1-year change in change in SF-36 – bodily pain (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 1.57 (0.20, 2.94)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in bodily pain score* *P*<0.05
Baseline to 1-year change in change in SF-36 – role emotional (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 3.06 (1.01, 5.10)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in role emotional score* *P*<0.05

Baseline to 1-year change in change in SF-36 – mental health (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 1.13 (0.21, 2.04)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in mental health score* *P*<0.05
Baseline to 1-year change in change in SF-36 – social functioning (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 2.56 (1.20, 3.92)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in social functioning score* *P*<0.05
Baseline to 1-year change in change in SF-36 – vitality (N=438)	1 g/dL increase in Hb from baseline to 6 months	MD 1.59 (0.55, 2.62)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in vitality score* *P*<0.05
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to an adult population initiation haemodialysis.			
Applicability			
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors conclude that "hemodialysis patients who attain higher hemoglobin concentration at 6 months, especially > 11 g/dL, have a better QoL at 1 year". Limitations of the study include the possibility of selection bias due to patients excluded from the analysis and potential residual confounding.			

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; MD, mean difference; NR, not reported; QoL, quality of life; SF-36, Short Form (36) Health Survey; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Portolés et al (2007) A prospective multicentre study of the role of anaemia as a risk factor in haemodialysis patients: the MAR study. Nephrol Dial Transplant 22: 500–507.		
Affiliation/Source of funds		
Fundación Hospital Alcorcón; Hospital Universitaro Gregorio Marañon, Marid; Hospital Universitario Reina Sofia, Córdoba; Spain. Partially supported by Johnson and Johnson.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	Spain/hospital
Risk factor/s assessed	Potential confounding variables measured	

Hb (continuous and categorical)	Age, sex, time on HD, cause of CKD, previous CV morbidity, previous vascular access events, non-CV comorbidity, type of access, albumin level, compliance with HD targets (Kt/V, nPCR, TAC urea) and time-dependent Hb.

Population characteristics (including size)
A representative sample of prevalent haemodialysis patients ≥ 18 years who started treatment between January 1999 and March 2001; at baseline 95% receiving EPO and 81% receiving iron; mean age ~ 64.4 years; male ~60.1%. N=1428

Length of follow-up	Outcomes measured
1 year	Mortality and hospitalisation (not included)

Method of analysis
Cox regression analysis was used. Only the analysis including adjustment for time-dependent Hb was used in this review (to correct for EPO dosing).
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Fair Description: Prospective cohort study; Used two-stage cluster sampling to identify a sample making up > 8% of prevalent patients in 2000; of 1710 in sample, 1428 completed follow-up (no details provided on patients who were not included in analysis); analysis adjusted for a number of potential confounders; follow-up 1 year.
RESULTS

Population	With risk factor	Without risk factor	
Available	1710		
Analysed	1428		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Mortality (N=1428)	1 g/dL increment in baseline Hb	OR 0.86 (0.76, 0.96)	*A 1 g/dL increment in baseline Hb is significantly associated with a 14% decrease in mortality risk* P<0.02
Mortality (N=1428)	1 g/dL increment in time-dependent Hb	OR 0.85 (0.75, 0.95)	*A 1 g/dL increment in time-dependent Hb is significantly associated with a 15% decrease in mortality risk* P<0.005

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to a prevalent population on haemodialysis, most of whom are receiving EPO and iron.
Applicability
This study was conducted in Spain. The results of this study may be applicable to the Australian setting.
Comments

The authors conclude that "anaemia is an independent risk factor that can predict survival…after adjustment for comorbidity, time on HD, cause of CKD, type of HD access, albumin level and Kt/V".

CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; dL, decilitre; EPO, erythropoietin; g, grams; Hb, haemoglobin; HD, haemodialysis; Kt/V, dialyzer clearance of urea X dialysis time/volume of distribution of urea; nPCR, normalised protein catabolic rate; OR, odds ratio; TAC, time-averaged concentration

STUDY DETAILS: Cohort study		
Citation		
Robinson et al (2005) Anemia and mortality in hemodialysis patients: accounting for morbidity and treatment variables updated over time. Kidney International 68: 2323–2330.		
Affiliation/Source of funds		
University of Pennsylvania School of Medicine, Philadelphia; University Renal Research and Education Association, Ann Arbor; US. The DOPPS in the US is supported by a research grant from Amgen without restriction on publications. Dr Robinson was supported in part by NIH grants.		
Study design	Level of evidence	Location/setting
Prospective cohort study (DOPPS)	Level II	US/Hospital
Risk factor/s assessed	Potential confounding variables measured	
Hb level	Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic cardiovascular disease, congestive heart failure, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, parathyroid hormone, white blood cell count, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis systolic blood pressure, currently prescribed nutritional supplement and hospitalised days.	
Population characteristics (including size)		
Random selection of patients undergoing haemodialysis; 56.2% aged ≥ 60 years; male 54.6%. N=5517		
Length of follow-up	Outcomes measured	
Median time at risk 13.4 months (3-month lag model)	Mortality	
Method of analysis		
Used Cox proportional hazards model.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Prospective cohort study; of 7300 who took part in the US DOPPS study, 7104 had one of more Hb values, 6167/5517/4610 were eligible for the 1/3/6 month lagged models; checked analysis to test if included subjects representative of the eligible subjects and they were; adjusted for a large number of potential confounders including EPO; performed analyses to check for median follow-up for 3 month lagged model 13.4 months.		
RESULTS		
Population	With risk factor	Without risk factor
Available	5517	
Analysed	Up to 3352	

Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
3-month lagged model 1				
Mortality (N=NR; total 3352) 3-month lagged model	Hb < 9 g/dL	Hb 11-<12 g/dL	HR 1.74 (1.24, 2.43)	A Hb < 9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 3352) 3-month lagged model	Hb 9-<10 g/dL	Hb 11-<12 g/dL	HR 1.25 (0.96, 1.63)	A Hb 9-<10 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 3352) 3-month lagged model	Hb 10-<11 g/dL	Hb 11-<12 g/dL	HR 1.22 (0.99, 1.49)	A Hb 10-<11 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 3352) 3-month lagged model	Hb 12-<13 g/dL	Hb 11-<12 g/dL	HR 0.90 (0.73, 1.13)	A Hb 12-<13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 3352) 3-month lagged model	Hb ≥13 g/dL	Hb 11-<12 g/dL	HR 1.04 (0.79, 1.36)	A Hb ≥13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
3-month lagged model 2				
Mortality (N=NR; total 3352) 3-month lagged model	Hb < 9 g/dL	Hb 11-<13 g/dL	HR 1.80 (1.29, 2.49)	A Hb < 9 g/dL is an independent risk factor for mortality compared with a Hb 11-<13 g/dL P=NR
Mortality (N=NR; total 3352) 3-month lagged model	Hb 9-<10 g/dL	Hb 11-<13 g/dL	HR 1.29 (1.01, 1.67)	A Hb 9-<10 g/dL is an independent risk factor for mortality compared with a Hb 11-<13 g/dL P=NR
Mortality (N=NR; total 3352) 3-month lagged model	Hb 10-<11 g/dL	Hb 11-<13 g/dL	HR 1.26 (1.04, 1.52)	A Hb 10-<11 g/dL is an independent risk factor for mortality compared with a Hb 11-<13 g/dL P=NR

Mortality (N=NR; total 3352) 3-month lagged model	Hb ≥13 g/dL	Hb 11-<13 g/dL	1.08 (0.83, 1.40)	A Hb ≥13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<13 g/dL P=NR
1-month lagged model				
Mortality (N=NR; total 2790) 1-month lagged model	Hb < 9 g/dL	Hb 11-<12 g/dL	HR 1.69 (1.14, 2.49)	A Hb < 9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 1-month lagged model	Hb 9-<10 g/dL	Hb 11-<12 g/dL	HR 1.46 (1.07, 2.00)	A Hb 9-<10 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 1-month lagged model	Hb 10-<11 g/dL	Hb 11-<12 g/dL	HR 1.23 (0.97, 1.56)	A Hb 10-<11 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 1-month lagged model	Hb 12-<13 g/dL	Hb 11-<12 g/dL	HR 0.97 (0.76, 1.24)	A Hb 12-<13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 1-month lagged model	Hb ≥13 g/dL	Hb 11-<12 g/dL	HR 1.10 (0.81, 1.49)	A Hb ≥13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
3-month lagged model 3				
Mortality (N=NR; total 2790) 3-month lagged model	Hb < 9 g/dL	Hb 11-<12 g/dL	HR 1.62 (1.09, 2.40)	A Hb < 9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 3-month lagged model	Hb 9-<10 g/dL	Hb 11-<12 g/dL	HR 1.21 (0.90, 1.64)	A Hb 9-<10 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR

Mortality (N=NR; total 2790) 3-month lagged model	Hb 10-<11 g/dL	Hb 11-<12 g/dL	HR 1.28 (1.02, 1.62)	A Hb 10-<11 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 3-month lagged model	Hb 12-<13 g/dL	Hb 11-<12 g/dL	HR 0.90 (0.70, 1.16)	A Hb 12-<13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 3-month lagged model	Hb ≥13 g/dL	Hb 11-<12 g/dL	HR 1.04 (0.77, 1.40)	A Hb ≥13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
6-month lagged model				
Mortality (N=NR; total 2790) 6-month lagged model	Hb < 9 g/dL	Hb 11-<12 g/dL	HR 1.59 (1.06, 2.37)	A Hb < 9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 6-month lagged model	Hb 9-<10 g/dL	Hb 11-<12 g/dL	HR 1.27 (0.95, 1.72)	A Hb 9-<10 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 6-month lagged model	Hb 10-<11 g/dL	Hb 11-<12 g/dL	HR 1.21 (0.97, 1.50)	A Hb 10-<11 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 6-month lagged model	Hb 12-<13 g/dL	Hb 11-<12 g/dL	HR 0.80 (0.63, 1.02)	A Hb 12-<13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Mortality (N=NR; total 2790) 6-month lagged model	Hb ≥13 g/dL	Hb 11-<12 g/dL	HR 0.79 (0.58, 1.08)	A Hb ≥13 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to an adult population on haemodialysis.				

Applicability
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.
Comments
The authors conclude that "our findings confirm the associations of Hb levels ≥ 11 g/dL with longer survival among maintenance HD patients, but show no additional survival advantage for patients with Hb levels ≥ 12 g/dL." The results were consistent across different lag-times and different reference ranges. They also looked effect modification by health status and found no significant interactions.

CI, confidence interval; dL, decilitre; g, grams; EPO, erythropoietin; ESRD, end-stage renal disease; Hb, haemoglobin; HD, haemodialysis; HR, hazard ratio; NR, not reported; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Stevens et al (2004) Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol 15: 770–779.		
Affiliation/Source of funds		
New England Medical Centre, Boston, US; University of British Columbia, Vancouver, Canada. Funding not stated.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level II	Canada/hospital
Risk factor/s assessed	Potential confounding variables measured	
Calcium, phosphate, parathyroid hormone and dialysis duration (also included Hb)	Analysis 1: age, gender, race, diabetes and dialysis type and duration. Analysis 2 (proportional hazards model): age, gender, diabetes, dialysis type, dialysis duration, race, dialysis adequacy (PRU), albumin, calcium, phosphate, parathyroid hormone. Analysis 3 (proportional hazards model): age, gender, diabetes, dialysis type, dialysis duration, race, dialysis adequacy (PRU), albumin, calcium and phosphate and parathyroid hormone (different combinations of different levels).	
Population characteristics (including size)		
Prevalent dialysis patients (haemodialysis or peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000; mean age 59.9; female 40.2%, Caucasian 57.9%. N=515		
Length of follow-up	Outcomes measured	
Median 31.6 months	Mortality (reported from each unit and validated using vital statistics from the province. Data censored for transplant and lost to follow-up).	
Method of analysis		
Cox proportional hazards model was used to identify important predictors of mortality. A series of models were created.		

INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Prospective hospital-based cohort study; 515 had complete data, no indication of how many excluded from analysis or what their characteristics were; 97 patients censored during the study due to transplant (N=88) or lost to follow-up (N=9); analysis adjusted for a number of known confounders as well as mineral metabolism markers; follow-up up to 3 years (median 32 months).			
RESULTS			
Population	With risk factor	Without risk factor	
Available	NR		
Analysed	515		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Mortality (N=515) Model 1	Hb (per 5 g/dL)	RR 0.93 (0.89, 0.97)	*A 5 g/dL difference in Hb is significantly associated with a 7% reduction in mortality risk.* P<0.001
Mortality (N=515) Model 2	Hb (per 5 g/dL)	RR 0.97 (0.92, 1.02)	*A 5 g/dL difference in Hb is <u>not</u> significantly associated with a change in mortality risk when continuous values of mineral metabolism parameters are included in the model.* P=0.194
Mortality (N=515) Model 3	Hb (per 5 g/dL)	RR 0.96 (0.91, 1.01)	*A 5 g/dL difference in Hb is <u>not</u> significantly associated with a change in mortality risk when categories of mineral metabolism parameters are combined and included in the model.* P=0.097
Mortality (N=125) Model 3 – dialysis duration < 6 months	Hb (per 5 g/dL)	RR 0.88 (0.78, 0.99)	*A 5 g/dL difference in Hb is significantly associated with a 12% reduction in mortality risk in patients on dialysis < 6 months when categories of mineral metabolism parameters are combined and included in the model* P=0.029

Mortality (N=117) Model 3 – dialysis duration 6–18 months	Hb (per 5 g/dL)	RR 0.98 (0.89, 1.01)	*A 5 g/dL difference in Hb is <u>not</u> significantly associated with a change in mortality risk in patients on dialysis 6–18 months when categories of mineral metabolism parameters are combined and included in the model.* P=0.710
Mortality (N=273) Model 3 – dialysis duration >18 months	Hb (per 5 g/dL)	RR 0.99 (0.92, 1.06)	*A 5 g/dL difference in Hb is <u>not</u> significantly associated with a change in mortality risk in patients on dialysis >18 months when categories of mineral metabolism parameters are combined and included in the model.* P=0.758
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a prevalent population of dialysis patients.			
Applicability			
This study was conducted in Canada. The results of this study are likely to be applicable to the Australian setting.			
Comments			
The authors make no specific conclusions regarding the association between Hb and mortality.			

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; NR, not reported; PRU, percent reduction of urea ; RR, relative risk;

STUDY DETAILS: Cohort study		
Citation		
Türk et al (2004) Quality of life in male hemodialysis patients. Nephron Clin Prac 96:c21-c27.		
Affiliation/Source of funds		
Selcuk University Medical School, Konya; Istanbul University, Istanbul; Turkey. Funding not reported.		
Study design	Level of evidence	Location/setting
Cross-sectional of a prospective cohort study	Level II	Turkey/hospital
Risk factor/s assessed	Potential confounding variables measured	
Hb (mean of last three measurements) and erectile dysfunction	Adjusted for variables found significant in the univariate analyses: age, occupation, education level and erectile dysfunction score.	
Population characteristics (including size)		
Men aged 18–65 on haemodialysis for at least 3 months. Mean age ~46 N=148		

Length of follow-up	Outcomes measured
-	QoL (SF-36 PCS and MCS)

Method of analysis
Multiple linear regression analysis with backward elimination was performed and variables found significant in univariate analysis were included.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Poor Description: Cross-sectional analysis of data from a prospective cohort study; of 511 haemodialysis patients, 148 male patients meeting the criteria were included (no details provided on male patients who did not meet criteria); variables found to be significant in univariate analysis considered in multivariate analysis; subjective outcome, unclear if patients aware of Hb status.
RESULTS

Population	With risk factor	Without risk factor	
Available	NR		
Analysed	148		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
SF-36 – physical component score (N=148) Men only	Hb g/dL	NR	*Haemoglobin level is significantly associated with physical component score* P=0.024
SF-36 – mental component score (N=148) Men only	Hb g/dL	NR	*Haemoglobin level is significantly associated with mental component score* P=0.021

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to a male population aged 18–65 years on haemodialysis for at least 3 months.
Applicability
This study was conducted in Turkey. The results of this study may be applicable to the Australian setting.
Comments
The authors conclude that Hb level is an independent variable (along with erectile dysfunction) that predicts the physical and mental component scores of the SF-36. They state that treatment for anaemia and erectile dysfunction may improve QoL in haemodialysis patients.

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; QoL, quality of life; PCS, Physical Component Summary; MCS, Mental Component Summary; NR, not reported; QoL, quality of life; SF-36, NR, not reported; Short Form (36) Health Survey

STUDY DETAILS: Cohort study			
Citation			
Yen et al (2010) Association between body mass and mortality in maintenance hemodialysis patients. Therapeutic Apheresis and Dialysis 14(4): 400–408.			
Affiliation/Source of funds			
Chang Gung Memorial Hospital, Taipei and Chang Gung University, Taoyuan, Taiwan. Funding not reported.			
Study design	Level of evidence	Location/setting	
Prospective cohort study	Level II	Taiwan/Hospital	
Risk factor/s assessed	Potential confounding variables measured		
Body mass and others (including Hb)	Variables considered if they were significant on univariate analysis and included age, BMI, previous CVD, diabetes, hypertension, haemodialysis duration, use of fistula, use of BCM dialyzer, nPCR, haemoglobin, albumin, creatinine, Log ferritin, phosphate, Log iPTH, HDL, LDL, Log hsCRP and cardiothoracic ratio. Only variables < 0.05 remained in model: age, diabetes, BMI, albumin, Log hsCRP, cardiothoracic ratio.		
Population characteristics (including size)			
Maintenance haemodialysis patients (excluding those with malignancies, active infections, surgery or transplant within 3 months, haemodialysis within 6 months, lead or cadmium poisoning). Mean age ~56, male ~46–50%. N=959			
Length of follow-up	Outcomes measured		
3 years	Mortality		
Method of analysis			
Multivariate Cox regression analysis.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Prospective cohort study; 959 included (no information of excluded subjects or those refusing to participate); adjusted for a number of variables that remained significant in stepwise analysis (excluded Hb as a variable); 3 year follow-up.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	NR		
Analysed	959		
Outcome (continuous)	Continuous measure	Risk estimate (95% CI)	Significance P-value
Mortality (N=959)	1 g/dL increment in Hb	Not included in model	*A 1 g/dL increment in Hb is not significantly associated with mortality* P=NR
EXTERNAL VALIDITY			
Generalisability			

This study is generalisable to a population of maintenance haemodialysis patients.
Applicability
This study was conducted in Taiwan. The results of this study may be applicable to the Australian setting.
Comments
The authors make no comments on the Hb results, other than to note that EPO use was highest in the subgroup of patients with the lowest Hb, those who were underweight.

BCM, biocompatible dialysis membrane; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; EPO, erythropoietin; Hb, haemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; nPCR, normalised protein catabolic rate; NR, not reported.

F2 Evidence summaries – Question 2

Medical population

Level I evidence

STUDY DETAILS: SR/MA				
Citation				
Carless et al (2010) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD002042. DOI: 10.1002/14651858.CD002042.pub2.				
Affiliation/Source of funds				
University of Newcastle, Newcastle, Australia; Institute of Clinical Evaluative Sciences, Toronto, Canada; Robert Wood Johnson Medical School, New Brunswick, US; Ottawa General Hospital, Ottawa, Canada; Scottish National Blood Transfusion Service, Edinburgh, UK; London School of Hygiene and Tropical Medicine, London, UK.				
Study design	Level of evidence	Location/setting		
Systematic review/meta-analysis of RCTs	Level I	Various		
Intervention/risk factor	Comparator			
Restrictive red blood cell transfusion (allogeneic or autologous)	Liberal red blood cell transfusion (allogeneic and/or autologous)			
Population characteristics				
Any eligible (N=17 RCTs and 3746 subjects). Included trauma, upper GI haemorrhage, critical care and surgery.				
Length of follow-up	Outcomes measured			
Not stated but mortality at 120 days included as an outcome	Mortality and cardiac events (MI, cardiac arrhythmias, cardiac arrest, pulmonary oedema and angina). Also requirement for allogeneic RBC transfusion, transfusion volume, Hct levels and hospital length of stay (not included here).			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Good Thorough literature search conducted; included RCTs only; quality of studies assessed; individual study results reported; meta-analysis conducted including all studies; heterogeneity assessed and discussed.				
RESULTS				
Outcome No. trials (No. patients)	Restrictive RBC transfusion n/N (%)	Liberal RBC transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity[a] P value (I^2)
All trials (includes critical care and surgery)				

< 15-day mortality 2 RCTs (N=821)	1/408 (0.2)	3/413 (0.7)	RR 0.44 (0.006, 2.96)	A restrictive RBC transfusion trigger does not significantly reduce < 15-day mortality compared with a liberal RBC transfusion trigger P=0.40 (Phet=0.84; I^2=0%)
30-day mortality 9 RCTs (N=2461)	113/1226 (9.2)	134/1235 (10.9)	RR 0.83 (0.66, 1.05)	A restrictive RBC transfusion trigger does not significantly reduce 30-day mortality compared with a liberal RBC transfusion trigger P=0.12 (Phet=0.65; I^2=0%)
60-day mortality 2 RCTs (N=922)	100/460 (21.7)	113/462 (24.5)	RR 1.09 (0.46, 2.60)	A restrictive RBC transfusion trigger does not significantly reduce 60-day mortality compared with a liberal RBC transfusion trigger P=0.85 (Phet=0.19; I^2=42%)
120-day mortality 1 RCT (N=69)	13/33 (39.4)	11/36 (30.6)	RR 1.29 (0.67, 2.47)	A restrictive RBC transfusion trigger does not significantly reduce120-day mortality compared with a liberal RBC transfusion trigger P=NR (Phet=NA)
Hospital mortality 4 RCTs (N=1409)	96/701 (13.7)	126/708 (17.8)	RR 0.78 (0.62, 0.98)	A restrictive RBC transfusion trigger does significantly reduce hospital mortality compared with a liberal RBC transfusion trigger P=0.031 (Phet=0.53; I2=0%)
ICU mortality 3 RCTs (N=736)	19/373 (5.1)	15/363 (4.1)	RR 1.15 (0.59, 2.23)	A restrictive RBC transfusion trigger does not significantly reduce ICU mortality compared with a liberal RBC transfusion trigger P=0.68 (Phet=0.52; I2=0%)

Mortality (unspecified follow-up) 1 RCT (N=214)	12/109 (11.0)	17/105 (16.2)	RR 0.68 (0.34, 1.35)	A restrictive RBC transfusion trigger does not significantly reduce mortality (over an unspecified follow-up period) compared with a liberal RBC transfusion trigger P=NR (Phet=NA)
Cardiac events 5 RCTs (N=1530)	113/762 (14.8)	152/768 (19.8)	RR 0.76 (0.57, 1.00)	A restrictive RBC transfusion trigger may significantly reduce cardiac events compared with a liberal RBC transfusion trigger P=0.049 (Phet=0.30; I^2=18%)
Myocardial infarction 7 RCTs (N=1868)	7/931 (0.8)	16/937 (1.7)	RR 0.50 (0.21, 1.21)	A restrictive RBC transfusion trigger does not significantly reduce myocardial compared with a liberal RBC transfusion trigger P=0.12 (Phet=0.54; I^2=0%)
Pulmonary oedema 4 RCTs (N=1633)	24/818 (2.9)	51/815 (6.3)	RR 0.49 (0.18, 1.31)	A restrictive RBC transfusion trigger does not significantly reduce pulmonary oedema compared with a liberal RBC transfusion trigger P=0.16 (Phet=0.30; I^2=19%)
Stroke 3 RCTs (N=242)	2/122 (1.6)	2/120 (1.7)	RR 0.98 (0.17, 5.52)	A restrictive RBC transfusion trigger does not significantly reduce stroke compared with a liberal RBC transfusion trigger P=0.98 (Phet=0.65; I^2=0%)
Pneumonia 4 RCTs (N=1679)	99/840 (11.8)	100/839 (11.9)	RR 1.00 (0.78, 1.29)	A restrictive RBC transfusion trigger does not significantly reduce pneumonia compared with a liberal RBC transfusion trigger P=0.98 (Phet=0.68; I^2=0%)

Thromboembolism 2 RCTs (N=204)	2/102 (2.0)	2/102 (2.0)	RR 0.95 (0.14, 6.36)	A restrictive RBC transfusion trigger does not significantly reduce thromboembolism compared with a liberal RBC transfusion trigger P=0.96 (Phet=0.37; I^2=0%)
Infection 4 RCTs (N=1788)	94/891 (10.5)	124/897 (13.8)	RR 0.76 (0.60, 0.97)	A restrictive RBC transfusion trigger significantly reduces infection compared with a liberal RBC transfusion trigger P=0.029 (Phet=0.43; I^2=0%)
EXTERNAL VALIDITY				
Generalisability				
The results of the overall analysis are generalisable to a broad population including medical, critical care and surgical patients.				
Applicability				
The studies included in the overall analysis were conducted in a number of different locations and are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that "the existing evidence supports the use of restrictive transfusion triggers in patients who are free of serious cardiac disease".				

CI, confidence interval; Hct, haematocrit; ICU, intensive care unit; MI, myocardial infarction; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio.

[a] 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%.

ACS

Level III evidence

STUDY DETAILS: Cohort study		
Citation		
Alexander et al (2008) Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. American Heart Journal 155: 1047–1053.		
Affiliation/Source of funds		
Duke University Medical Center, Durham, US; University of Buffalo School of Medicine and Biological Sciences, Buffalo, US. CRUSADE is funded by the Schering-Plough Corporation. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership provides additional funding support. Millennium Pharmaceuticals Inc also funded this work. This work was also supported in part by a grant from the National Institute on Aging.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	US/hospital

Risk factor/s assessed	Potential confounding variables measured
Transfusion vs no transfusion (transfusion defined as any non-autologous transfusion of whole or packed RBCs)	Analysis 1: adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission) Analysis 2: above + baseline HCT and transfusion by nadir HCT interaction.
Population characteristics (including size)	
Patients with NSTE ACS. Patients were not eligible if they presented > 24 hours after their last symptoms. N=61,874. Patients were excluded if they transferred to another hospital (N=6073), had missing data on transfusion (N=356), nadir HCT (N=4486), had data entry errors (N=22) or had CABG (N=6695). The final population was N=44,242. .	
Length of follow-up	Outcomes measured
Hospitalisation	Mortality (also included death or MI, CHF or shock).
Method of analysis	
Logistic generalised estimating equations were used to estimate the association of transfusion with mortality in each nadir HCT group.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: Retrospective cohort study; 72% of potentially eligible subjects included in analysis; no consideration of potential differences between included and excluded population; analysis adjusted for a large number of potential confounders; in-hospital follow-up.	

RESULTS				
Population	With risk factor		Without risk factor	
Available	61,874			
Analysed	4610		39,632	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality (nadir HCT < 24%) N=1633	RBC transfusion	No RBC transfusion	Analysis 1: OR 0.75 (0.50, 1.12)	*Transfusion is <u>not</u> an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT < 24%* P=NR
Mortality (nadir HCT < 24%) N=1633	RBC transfusion	No RBC transfusion	Analysis 2: OR 0.67 (0.45, 1.02)	*Transfusion is <u>not</u> an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT < 24%* P=NR

Mortality (nadir HCT 24.1% to 27%) N=3263	RBC transfusion	No RBC transfusion	Analysis 1: OR 1.01 (0.79, 1.28)	*Transfusion is <u>not</u> an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT 24.1% to 27%* P=NR
Mortality (nadir HCT 24.1% to 27%) N=3263	RBC transfusion	No RBC transfusion	Analysis 2: OR 1.01 (0.79, 1.30)	*Transfusion is <u>not</u> an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT 24.1% to 27%* P=NR
Mortality (nadir HCT 27.1% to 30%) N=4919	RBC transfusion	No RBC transfusion	Analysis 1: OR 1.14 (0.90, 1.46)	*Transfusion is <u>not</u> an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT 27.1% to 30%* P=NR
Mortality (nadir HCT 27.1% to 30%) N=4919	RBC transfusion	No RBC transfusion	Analysis 2: OR 1.18 (0.92, 1.50)	*Transfusion is <u>not</u> an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT 27.1% to 30%* P=NR
Mortality (nadir HCT > 30%) N=34,427	RBC transfusion	No RBC transfusion	Analysis 1: OR 2.89 (1.85, 4.51)	*Transfusion is an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT > 30%* P=NR
Mortality (nadir HCT > 30%) N=34,427	RBC transfusion	No RBC transfusion	Analysis 2: OR 3.47 (2.30, 5.23)	*Transfusion is an independent risk factor for mortality in NSTE-ACS patients with a nadir HCT > 30%* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with non-ST-segment elevation ACS.				
Applicability				
This study was conducted in the US. The results of this study are likely to be applicable to the Australian setting.				

Comments
The authors conclude that "the observed association between transfusion and adverse events is neutral in the nadir HCT range where transfusions are most often given and trends strongly to benefit when nadir HCT is < 24%". They also note that "although rare, those transfused with nadir HCT of 27% to 30%....or HCT of > 30%...had higher mortality".

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; ECG, electrocardiograph; HCT, haematocrit; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; PCI, Percutaneous coronary intervention; RBC, red blood cell; SBP, systolic blood pressure; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Rao et al (2004) Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 282: 1555–1562.		
Affiliation/Source of funds		
Duke Clinical Research Institute, Durham, US; University of Alberta, Edmonton, Canada; Cleveland Clinic Foundation, Cleveland, US. Supported by Duke Clinical Research Institute.		
Study design	Level of evidence	Location/setting
Prospective cohort analysis of data from 3 RCTs	Level III-2	Various/hospital

Risk factor/s assessed	Potential confounding variables measured
Blood transfusion vs no blood transfusion	Cox-regression analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit. Landmark analysis adjusted for: above plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period. Predicted probabilities analysis adjusted for: above plus nadir Hct
Population characteristics (including size)	
Patients with NSTE-ACS. Mean age ~ 65 years; female ~ 35%; African-American ~ 4%. N=24,112	
Length of follow-up	Outcomes measured
30 days	30-day mortality 30-day mortality or MI
Method of analysis	
Three analyses were carried out: (i) Cox regression analysis incorporating transfusion as a time-dependent covariate; (ii) a landmark analysis dividing the study into seven 24-hour time periods; and (iii) logistic regression model incorporating nadir Hct as a continuous variable.	

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Cohort analysis of data from three RCTs so unlikely to be substantial follow-up bias; analysis performed in three ways and adjusted for a large number of potential confounding variables; mortality measured over short time period.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR			
Analysed	2401		21,711	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Analysis 1: Cox regression analysis				
30-day mortality (N=24,112)	Blood transfusion 192/2401 (8.0)	No blood transfusion 669/21,711 (3.1)	HR 3.94 (3.26, 4.75)	*Blood transfusion is significantly associated with 30-day mortality in patients with NSTE-ACS* P=NR
30-day mortality/recurrent MI (N=24,112)	Blood transfusion 702/2401 (29.2)	No blood transfusion 2176/21,711 (10.0)	HR 2.92 (2.55, 3.35)	*Blood transfusion is significantly associated with 30-day mortality/recurrent MI in patients with NSTE-ACS* P=NR
Analysis 2: Landmark analysis				
30-day mortality First 24 hours (N=20,688 at risk)	Blood transfusion	No blood transfusion	NR	Blood transfusion is not significantly associated with 30-day mortality during the first 24 hours in patients with NSTE-ACS P=NR
30-day mortality Second 24 hours (N=20,464 at risk)	Blood transfusion	No blood transfusion	NR	Blood transfusion is not significantly associated with 30-day mortality during the second 24 hours in patients with NSTE-ACS P=NR

30-day mortality Third 24 hours (N=20,256 at risk)	Blood transfusion	No blood transfusion	NR	Blood transfusion is significantly associated with 30-day mortality during the third 24 hours in patients with NSTE-ACS P=NR
30-day mortality Fourth 24 hours (N=20,013 at risk)	Blood transfusion	No blood transfusion	NR	Blood transfusion is not significantly associated with 30-day mortality during the fourth 24 hours in patients with NSTE-ACS P=NR
30-day mortality Fifth 24 hours (N=19,816 at risk)	Blood transfusion	No blood transfusion	NR	Blood transfusion is significantly associated with 30-day mortality during the fifth 24 hours in patients with NSTE-ACS P=NR
30-day mortality Sixth 24 hours (N=19,625 at risk)	Blood transfusion	No blood transfusion	NR	Blood transfusion is not significantly associated with 30-day mortality during the sixth 24 hours in patients with NSTE-ACS P=NR
30-day mortality Seventh 24 hours (N=19,450 at risk)	Blood transfusion	No blood transfusion	NR	Blood transfusion is not significantly associated with 30-day mortality during the seventh 24 hours in patients with NSTE-ACS P=NR
Analysis 3: Logistic regression analysis				
30-day mortality Nadir Hct 20% (N=NR)	Blood transfusion	No blood transfusion	OR 1.59 (0.95, 2.66)	Blood transfusion is not significantly associated with 30-day mortality in patients with NSTE-ACS with a nadir Hct of 20% P=NR
30-day mortality Nadir Hct 25% (N=NR)	Blood transfusion	No blood transfusion	OR 1.13 (0.70, 1.82)	Blood transfusion is not significantly associated with 30-day mortality in patients with NSTE-ACS with a nadir Hct of 25% P=NR

30-day mortality Nadir Hct 30% (N=NR)	Blood transfusion	No blood transfusion	OR 168 (7.49, 3798)	Blood transfusion is significantly associated with 30-day mortality in patients with NSTE-ACS with a nadir Hct of 30% P=NR
30-day mortality Nadir Hct 35% (N=NR)	Blood transfusion	No blood transfusion	OR 292 (10.3, 8274)	Blood transfusion is significantly associated with 30-day mortality in patients with NSTE-ACS with a nadir Hct of 35% P=NR

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to an adult population with NSTE-ACS. The authors note that results from this RCT cohort may not be generalisable to "real-world" patients.
Applicability
This study was conducted in a number of locations including the US. The results of this study are likely applicable to the Australian setting.
Comments
The authors conclude that "blood transfusion in the setting of ACS was associated with an increased risk of short-term mortality". They note this risk persisted despite adjustment for a large number of potential confounders, and using different analysis techniques. While they note that an RCT is warranted to guide clinical practice, they "caution against the routine use of blood transfusion to maintain arbitrary haematocrit levels in stable patients with ischaemic heart disease". The authors note a number of limitations of their study including (i) the fact that it is a post-hoc cohort analysis of RCT data; (ii) the potential for residual confounding; and (iii) the inability to explore the indications for and appropriateness of transfusions.

CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CK, creatinine kinase; DBP, diastolic blood pressure; ECG, electrocardiograph; HCT, haematocrit; HR, hazard ratio; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PCI, Percutaneous coronary intervention; PVD, Peripheral vascular disease; RCT, randomised controlled trial; SBP, systolic blood pressure; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Sabatine et al (2005) Association of haemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 111: 2042–2049.		
Affiliation/Source of funds		
TIMI Study Group; Brigham and Women's Hospital, Boston, US; Amgen Inc, Thousand Oaks, US. Statistical analyses supported by Amgen Inc. Dr Sabatine is supported in part by National Heart, Lung and Blood Institute grants.		
Study design	Level of evidence	Location/setting
Cohort analysis of 16 RCTs	Level III-2	Hospital/Various
Risk factor/s assessed	Potential confounding variables measured	

Hb (includes whole or packed RBC transfusion)	Age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, β-blocker, angiotensin receptor blocker, or hypolipidemic use, index revascularisation, transfusion, transfusion and Hb interaction and bleeding (NSTE-ACS) + anterior location of index MI (STEMI only addition)
Population characteristics (including size)	
Patients divided into two groups of those with STEMI or NSTE-ACS: (i) STEMI – mean age 60.2 years, 24.2% female, Caucasian 91.7% (N=25,419); (ii) NSTE-ACS – mean age 62.0 years, female 33%, Caucasian 88.2% (14,503)	
Length of follow-up	Outcomes measured
30 days	STEMI – cardiovascular mortality and congestive heart failure; NSTE-ACS – cardiovascular mortality, MI and recurrent myocardial ischaemia.
Method of analysis	
Multivariable logistic regression analysis was used to evaluate the independent relationship between haemoglobin and cardiovascular endpoints.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: Cohort analysis of data from 16 RCTs; patients included in analysis were those with baseline haemoglobin data available, no mention of how many were excluded from the analysis; analysis adjusted for a large number of potential confounders which were those in which there was > 80% data availability and that showed an association with baseline Hb (P<0.025) or were known to be of clinical importance; method of outcome data collection not reported; follow-up 30 days.	
RESULTS	

Population	With risk factor		Without risk factor	
Available	NR			
Analysed	STEMI – 25,419; NSTE-ACS – 14,503			
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
30-day cardiovascular mortality (N=1441) STEMI with Hb < 12 g/dL	NR	NR	OR 0.42 (0.20, 0.89)	Whole or pRBC transfusion is significantly associated with 30-day cardiovascular mortality in patients with STEMI with a Hb < 12 g/dL P=NR

30-day cardiovascular mortality (N=23,978) STEMI with Hb ≥ 12 g/dL	NR	NR	OR 1.42 (0.94, 2.17)	Whole or pRBC transfusion is <u>not</u> associated with 30-day cardiovascular mortality in patients with STEMI with a Hb ≥ 12 g/dL P=NR
30-day cardiovascular mortality/MI/recurrent ischaemia (N=14,503) NSTE-ACS	NR	NR	OR 1.54 (1.14, 2.09)	Whole or pRBC transfusion is significantly associated with 30-day cardiovascular mortality in patients with NSTE-ACS patients P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a broad spectrum of patients with STEMI and NSTE-ACS.				
Applicability				
This study was conducted in a wide range of countries. The results of this study are likely to be generalisable to the Australian setting.				
Comments				
The authors conclude that in a "broad spectrum of patients with ACS, we found large, highly statistically significant, and independent associations between low haemoglobin concentrations and adverse cardiovascular outcomes". In particular they note that the increased risk began at Hb < 14 g/dL for patients with STEMI and at < 11 g/dL for patients with NTSE-ACS. The authors note a number of limitations of their study including (i) the fact that the data came from clinical trials, however they state that because the inclusion and exclusion criteria differed between the trials, this has strengthened the generalisability of their findings; (ii) the cause of anaemia was unknown, although patients with recent bleeding, known bleeding diathesis or significant renal or haematologic-oncological diseases were excluded from the trials; (iii) they did not measure erythropoietin so some observations may be due to high or low erythropoietin rather than anaemia; and (iv) there is the possibility of residual confounding although they note this is likely to be small given the large number of potential confounders assessed and included in the analyses. One additional concern identified during the review is why different Hb levels were used as the reference level in the analyses, and in particular why 14–15 was used in the STEMI patients and 15–16 was used in the NTSE-ACS patients.				

ACEI, angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass graft; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; RCT, randomised controlled trial; STEMI, ST-segment elevation myocardial infarction; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Shishehbor et al (2009) Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2:46–53.		
Affiliation/Source of funds		
Cleveland Clinic, Cleveland, US; University of Michigan, Ann Arbor, US; National Institute of Health, Bethesda, US; The Scripps Research Institute, La Jolla, US. Dr Shishehbor is supported in part by the National Institutes of Health.		
Study design	Level of evidence	Location/setting

Cohort analysis of a RCT	Level III-2		Various (US, Canada, Europe, Australia and New Zealand)/hospital	
Risk factor/s assessed		Potential confounding variables measured		
Blood transfusion vs no blood transfusion. Blood transfusion defined as whole blood or packed RBCs.		Analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital). Also adjusted for nadir Hb in propensity matched analysis.		
Population characteristics (including size)				
Patients with STEMI (excluded those who were part of a sub study of CABG); mean age ~ 63 years; female ~ 24%; African American ~ 3%. N=3575				
Length of follow-up		Outcomes measured		
Up to 1 year		30-day, 6-month and 1-year mortality; 30-day, 6-month and 1-year MI		
Method of analysis				
Carried out two analyses: (i) Cox proportional hazards analysis using transfusion as a time-dependent covariate; and (ii) using propensity score and matching. A sensitivity analysis was also carried out to see the magnitude of hidden bias that would have to be present to explain the associations observed.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Cohort analysis of data from a RCT; of the 4131 subjects with STEMI in the trial, 53 were excluded for missing transfusion data and 503 who were part of a CABG study were excluded; analysis adjusted for a large number of potential confounding variables; follow-up up to 1 year.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR			
Analysed	307		3268	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Analysis 1: Cox proportional hazards analysis				
30-day mortality (N=3575)	Blood transfusion	No blood transfusion	HR 3.89 (2.66, 5.68)	*Blood transfusion is a significant predictor of 30-day mortality in patients with STEMI* P<0.001
6-month mortality (N=3538)	Blood transfusion	No blood transfusion	HR 3.63 (2.67, 4.95)	*Blood transfusion is a significant predictor of 6-month mortality in patients with STEMI* P<0.001

1-year mortality (N=3465)	Blood transfusion	No blood transfusion	HR 3.03 (2.25, 4.08)	*Blood transfusion is a significant predictor of 6-month mortality in patients with STEMI* P<0.001
30-day MI (N=3575)	Blood transfusion	No blood transfusion	HR 3.44	*Blood transfusion is a significant predictor of 30-day MI in patients with STEMI* P<0.001
6-month MI (N=3538)	Blood transfusion	No blood transfusion	HR 2.69	*Blood transfusion is a significant predictor of 6-month MI in patients with STEMI* P<0.001
1-year MI (N=3465)	Blood transfusion	No blood transfusion	NR	*Blood transfusion is <u>not</u> a significant predictor of 6-month MI in patients with STEMI* P<0.001
Analysis 2: Propensity score and matching				
30-day mortality (N=943)	Blood transfusion	No blood transfusion	HR 5.44 (3.21, 9.22)	*Blood transfusion is a significant predictor of 30-day mortality in patients with STEMI* P<0.001
6-month mortality (N=958)	Blood transfusion	No blood transfusion	HR 4.81 (3.00, 7.71)	*Blood transfusion is a significant predictor of 6-month mortality in patients with STEMI* P<0.001
1-year mortality (N=958)	Blood transfusion	No blood transfusion	HR 3.10 (2.18, 4.40)	*Blood transfusion is a significant predictor of 1-year mortality in patients with STEMI* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to an adult population with STEMI.				
Applicability				
This study was conducted in a number of countries including Australia and New Zealand (6.1%). The results of this study are directly applicable to the Australian setting.				
Comments				

The authors conclude that "in patients with STEMI, blood transfusion was an independent predictor of both short- and long-term mortality". In their sensitivity analysis they showed that the results were "highly insensitive to bias and that hidden bias has to be enormous to alter our conclusions". They note a number of limitations of their study including (i) the fact it is a post-hoc cohort analysis of RCT data; (ii) the possibility of residual confounding; and (iii) the fact that the cohort is now outdated and that pharmacological and interventional therapies have changed since then.

CABG, coronary artery bypass graft; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; HR, hazard ratio; NR, not reported; PCI, Percutaneous coronary intervention; PVD, Peripheral vascular disease; RBC, red blood cell; RCT, randomised controlled trial; STEMI, ST-segment elevation myocardial infarction; US, United States of America.

STUDY DETAILS: Cohort study		
Citation		
Wu et al (2001) Blood transfusion in elderly patients with acute myocardial infarction. New England Journal of Medicine 345(17): 1230–1236.		
Affiliation/Source of funds		
Brown University Medical School, Providence; Yale University School of Medicine, New Haven; Yale-New Haven Hospital Center for Outcomes Research and Evaluation, New Haven; Qualidigm, Middletown, US. Supported by a contract with the Health Care Financing Administration.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	US/hospital
Risk factor/s assessed	Potential confounding variables measured	
Blood transfusion vs no blood transfusion	Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.	
Population characteristics (including size)		
Aged ≥ 65 years with confirmed acute MI (and without terminal illness/metastatic cancer, bleeding or haemorrhage or surgery). Mean age 77.8 years; female 54%, 89.5% Caucasian. N=78,974		
Length of follow-up	Outcomes measured	
30 days	30-day mortality (also in-hospital shock, CHF and length of hospitalisation).	
Method of analysis		
Logistic regression model.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Retrospective hospital-based cohort; cohort taken from a larger Medicare-based study cohort; of 234,769 subjects, 17,593 excluded for being < 65 years, 45,349 for not having confirmed acute MI, 23,773 for being readmitted for MI; 81,306 excluded for being transferred to or from the study hospital; other reasons for exclusion included co-morbidities, high or implausible Hct levels; in total 33.6% of the original cohort were included in the study; analysis adjusted for a large number of potential confounders, many of which were identified via univariate and stepwise analyses; follow-up 30 days.		
RESULTS		

Population	With risk factor		Without risk factor	
Available				
Analysed	3680		75,294	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
All subjects				
30-day mortality Hct 5.0–24.0% (N=380)	Blood transfusion	No blood transfusion	OR 0.22 (0.11, 0.45)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 5.0–24.0%* P=NR
30-day mortality Hct 24.1–27.0% (N=838)	Blood transfusion	No blood transfusion	OR 0.48 (0.34, 0.69)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 24.1–27.0%* P=NR
30-day mortality Hct 27.1–30.0% (N=2106)	Blood transfusion	No blood transfusion	OR 0.60 (0.47, 0.76)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 27.1–30.0%* P=NR
30-day mortality Hct 30.1–33.0% (N=4848)	Blood transfusion	No blood transfusion	OR 0.69 (0.53, 0.89)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 30.1–33.0%* P=NR
30-day mortality Hct 33.1–36.0% (N=9885)	Blood transfusion	No blood transfusion	OR 1.13 (0.89, 1.44)	*Blood transfusion is <u>not</u> associated with 30-day mortality in elderly patients with AMI and a Hct 33.1–36.0%* P=NR
30-day mortality Hct 36.1–39.0% (N=16,218)	Blood transfusion	No blood transfusion	OR 1.38 (1.05, 1.80)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 36.1–39.0%* P=NR

30-day mortality Hct 39.1–48.0% (N=44,699)	Blood transfusion	No blood transfusion	OR 1.46 (1.18, 1.81)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 39.1–48.0%* P=NR
Excluding patients who died in the first 2 days				
30-day mortality Hct 5.0–24.0% (N=NR)	Blood transfusion	No blood transfusion	OR 0.36 (0.15, 0.83)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 5.0–24.0%* P=NR
30-day mortality Hct 24.1–27.0% (N=NR)	Blood transfusion	No blood transfusion	OR 0.69 (0.47, 1.01)	*Blood transfusion may be associated with 30-day mortality in elderly patients with AMI and a Hct 24.1–27.0%* P=NR
30-day mortality Hct 27.1–30.0% (N=NR)	Blood transfusion	No blood transfusion	OR 0.75 (0.58, 0.96)	*Blood transfusion is significantly associated with 30-day mortality in elderly patients with AMI and a Hct 27.1–30.0%* P=NR
30-day mortality Hct 30.1–33.0% (N=NR)	Blood transfusion	No blood transfusion	OR 0.98 (0.76, 1.25)	*Blood transfusion is not associated with 30-day mortality in elderly patients with AMI and a Hct 30.1–33.0%* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to an elderly population with AMI.				
Applicability				
This study was conducted in the US. The results of this study are likely applicable to the Australian setting.				
Comments				
The authors conclude that "blood transfusion is associated with a lower short-term mortality rate among elderly patients with acute myocardial infarction if the haematocrit is 30.0 percent or lower and may be effective in patients with a haematocrit as high as 33.0 percent on admission".				

AMI, acute myocardial infarction; APACHE II, Acute Physiology and Chronic Health Evaluation II; CHF, congestive heart failure; CI, confidence interval; HCT, haematocrit; HR, heart rate; MAP, mean arterial pressure; MI, myocardial infarction; NR, not reported; OR, odds ratio; US, United States of America.

STUDY DETAILS: Cohort study

Citation				
Yang et al (2005) The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes. Journal of the American College of Cardiology 46(8): 1490–1495.				
Affiliation/Source of funds				
Duke University Medical Center, Durham; Kaiser-Permanente San Francisco Medical Center, San Francisco; University of Cincinnati School of Medicine, Cincinnati; University of North Carolina, Chapel Hill; US. The CRUSADE trial is funded by Millennium Pharmaceuticals and Schering-Plough; Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership provides an unrestricted grant in support of the programme.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		US/hospital	
Risk factor/s assessed		Potential confounding variables measured		
Blood transfusion vs no blood transfusion		Adjusted for: patients demographics (age, gender, BMI, race), cardiac risk factors (family history of CAD, hypertension, diabetes, current/recent smoker, hypercholesterolaemia), medical co-morbidities (renal insufficiency, previous MI, previous PCI, previous CABG, previous CHF, previous stroke), presenting characteristics (ST-segment depression, ST-segment elevation, positive cardiac marker, signs of CHF at presentation, HR, SBP) and socioeconomic status (insurance status).		
Population characteristics (including size)				
Adults with symptoms referable to MI lasting at least 10 mins combined with positive cardiac biomarkers or ischaemic ST-segment ECG changes, excluding those who underwent CABG while hospitalised; Mean age ~68; female ~ 41%, Caucasian ~ 80%. N=85,111				
Length of follow-up		Outcomes measured		
In-hospital		Death and death/MI		
Method of analysis				
Multivariate analysis				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Retrospective hospital-based cohort study; population taken from the CRUSADE study from Jan 2001 to Mar 2004; of the 98,571 eligible, 74,271 had complete transfusion data, had not undergone CABG while hospitalised and had not been transferred to another hospital; analysis adjusted for a large number of potential confounders although Hct doesn't appear to have been included; follow-up while in hospital.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	12,724		72,387	
Analysed	74,271			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value

In-hospital mortality (N=74,271)	Blood transfusion 11.5%	No blood transfusion 3.8%	OR 1.67 (1.48, 1.88)	*Blood transfusion is significantly associated with in-hospital mortality in patients with NSTE-ACS who haven't undergone CABG while hospitalised* P=NR
In-hospital mortality/MI (N=74,271)	Blood transfusion 13.4%	No blood transfusion 5.8%	OR 1.44 (1.30, 1.60)	*Blood transfusion is significantly associated with in-hospital mortality/MI in patients with MI who haven't undergone CABG while hospitalised* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with NSTE-ACS who have not undergone CABG while hospitalised.				
Applicability				
This study was conducted in the US. The results of this study are likely applicable to the Australian setting.				
Comments				
The authors conclude that "patients who undergo transfusion are sicker at baseline and experience a higher risk of adverse outcomes than their nontransfused counterparts". They note a number of limitations including (i) the timing of the transfusion, and (ii) the possibility of residual confounding.				

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; ECG, electrocardiograph; HR, heart rate; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; PCI, Percutaneous coronary intervention; SBP, systolic blood pressure; US, United States of America.

Heart failure

Level III evidence

STUDY DETAILS: Cohort study		
Citation		
Garty et al (2009) Blood transfusion for acute decompensated heart failure – friend or foe? American heart Journal 158: 653–658.		
Affiliation/Source of funds		
Rabin Medical Center, Beilinson Camus, Petah Tiqwa, Israel; Tel Aviv University, Tel Aviv, Israel; Sheba Medical Center, Tel Hashomer, Israel; Tel Aviv Sourasky Medical Center, Israel; Hillel Yaffe Medical Centre, Hadera, Israel; Bikur Cholim Hospital, Jerusalem, Israel; Kaplan Medical Center		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level III-2	Israel/hospital
Risk factor/s assessed	Potential confounding variables measured	

Blood transfusion vs no blood transfusion			Adjusted for: age, sex, hypertension, diabetes mellitus, current smoking, concurrent ACS, heart rate, SBP, LVEF, eGFR and propensity score.	
Population characteristics (including size)				
Patients with heart failure admitted to cardiology or internal medicine wards who had acute decompensated heart failure. Mean age ~74 years, Male ~ 55%. N=2335				
Length of follow-up			Outcomes measured	
Up to 4 years			Mortality (during hospitalisation, 30 day, 1 year and 4 year).	
Method of analysis				
A logistic regression model was used for in-hospital and 30-day mortality and a Cox proportional hazards model was used for 1 and 4 year mortality.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective nationwide hospital-based survey; of 4102 HF subjects, 2335 had ADHF and were included; outcome was determined in 99% of patients in first 12 months; outcome measured via database or by cross-referencing with the Israel National Population Death Register; up to 4 years follow-up.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	2335			
Analysed	166		2169	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
In-hospital mortality (N=2335)	Blood transfusion 18/166 (10.8)	No blood transfusion 113/2169 (5.2)	OR 0.48 (0.21, 1.11)	*Blood transfusion <u>may</u> be significantly associated with in-hospital mortality in patients with ADHF* P=0.08
30-day mortality (N=2317)[a]	Blood transfusion 18/164 (11.0)	No blood transfusion 183/2153 (8.5)	OR 0.29 (0.13, 0.64)	*Blood transfusion is significantly associated with 30-day mortality in patients with ADHF* P=0.02
1-year mortality (N=2325)[a]	Blood transfusion 65/164 (39.6)	No blood transfusion 616/2161 (28.5)	HR 0.74 (0.50, 1.09)	*Blood transfusion is <u>not</u> significantly associated with 1-year mortality in patients with ADHF* P=0.12
4-year mortality (N=2321)[a]	Blood transfusion 114/164 (69.5)	No blood transfusion 1284/2157 (59.5)	HR 0.86 (0.64, 1.14)	*Blood transfusion is <u>not</u> significantly associated with 4-year mortality in patients with ADHF* P=0.29
EXTERNAL VALIDITY				

Generalisability
The results of this study are generalisable to a population with acute decompensated heart failure.
Applicability
This study was conducted using data from all public hospitals in Israel. The results of this study are likely applicable to the Australian setting.
Comments
The authors conclude that the patients included in this study who received blood transfusion had "worse clinical features and unadjusted outcomes, but BT per se seemed to be safe and perhaps even beneficial".

ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; OR, odds ratio; SBP, systolic blood pressure.

[a] N calculated for each measurement based on percentages in Table III of the publication.

Cancer

Level III evidence

STUDY DETAILS: Cohort study				
Citation				
Khorana et al (2008) Blood transfusions, thrombosis and mortality in hospitalised patients with cancer. Archives of Internal Medicine 168(21): 2377–2381.				
Affiliation/Source of funds				
University of Rochester, Rochester, US; Duke University Medical Center and Duke Comprehensive Cancer Center, Durham, US. This study was supported, in part, by a grant from the National Cancer Institute and by grants from the National Heart, Lung and Blood Institute.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		US/hospital	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion vs no RBC transfusion		Adjusted for: age, gender, site or type of cancer, race/ethnicity, chemotherapy, venous catheters, and comorbidities including anaemia, infection, renal disease and lung disease.		
Population characteristics (including size)				
Adult patients with cancer admitted to one of 60 academic medical centres in the US; 43.4% > 65 years; 49.4% female; 70.9% Caucasian. N=504,208.				
Length of follow-up		Outcomes measured		
During hospitalisation.		Mortality, VTE/ATE		
Method of analysis				
Multivariate logistic regression analysis used.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Retrospective hospital-based cohort study with disease, intervention and outcome data collected via ICD-9 codes; measures taken to reduce bias caused by this including excluding sites with under or inconsistent reporting of transfusion, and excluding subjects with a primary diagnosis of VTE or ATE; regression analysis used to identify potential confounders; not able to check for ESA use as a potential confounder; follow-up while in hospital.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR			
Analysed	58,814		445,394	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value

VTE (N=504,208)	RBC transfusion	No RBC transfusion	OR 1.60 (1.53, 1.67)	*RBC transfusion is significantly associated with VTE in hospitalised patients with cancer* P=<0.001
ATE (N=504,208)	RBC transfusion	No RBC transfusion	OR 1.53 (1.46, 1.61)	*RBC transfusion is significantly associated with ATE in hospitalised patients with cancer* P=<0.001
In-hospital mortality (N=503,185)	RBC transfusion	No RBC transfusion	OR 1.34 (1.29, 1.38)	*RBC transfusion is significantly associated with in-hospital mortality in hospitalised patients with cancer* P=<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to hospitalised patients with cancer.				
Applicability				
This study was conducted in 60 academic medical centres in the US. The results of this study are likely applicable to Australia.				
Comments				
The authors conclude that RBC transfusion (and platelet transfusion) is associated with increased risk of VTE, ATE and mortality in hospitalised patients with cancer. They also note that further investigation is necessary to determine if this relationship is causal. They note a number of limitations of their study including (i) that it relies on administrative coding, although they have taken a number of measures to try and minimise any bias associated with this; (ii) they are unable to examine whether use of ESAs may have confounded the results; and (iii) an inability to determine the time of administration of transfusion in relation to the development of VTE or ATE, although measures were taken to minimise this potential bias.				

ATE, arterial thromboembolism; CI, confidence interval; ESA, erythropoiesis stimulating agent; OR, odds ratio; RBC, red blood cell; US, United States of America; VTE, venous thromboembolism.

Acute gastrointestinal haemorrhage

Level II evidence

STUDY DETAILS: RCT		
Citation		
Blair et al (1986) Effect of early blood transfusion on gastrointestinal haemorrhage. British Journal of Surgery 73: 783–785.		
Affiliation/Source of funds		
Charing Cross and Westminster Medical School, London, UK; Crawley Hospital, Crawley, UK. Financial assistance provided by the Crawley and Jersey Research Fund.		
Study design	Level of evidence	Location/setting

RCT	Level II		UK/hospital	
Intervention		Comparator		
Blood transfusion in first 24 hours		No blood transfusion in first 24 hours		
Population characteristics				
Patients with acute severe upper GI haemorrhage. Mean age ~ 62 years; male:femal ration 2:1; Hb < 8 g/dL 6/24 in transfusion arm and 5/26 in no transfusion arm (these subjects were transfused). N=50.				
Length of follow-up		Outcomes measured		
Not stated (assumed to be during hospitalisation).				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Randomised but no method stated; not double-blind but objective outcome (mortality); appears to be no loss to follow-up; ITT analysis carried out; 5/26 patients randomised to no transfusion in 24 hours arm received transfusion due to Hb < 8 g/dL; study underpowered to detect a difference in mortality. Poor				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	24		26	
Efficacy analysis (ITT)	24		26	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NA		NA	
Outcome	Blood transfusion in first 24 hours (liberal) n/N (%)	No blood transfusion in first 24 hours (restrictive) n/N (%)	Risk estimate (95% CI)	Significance P-value
Mortality 1 RCT (N=50)	2/24 (8.3)	0/26 (0)	NR	Blood transfusion in the first 24 hours does <u>not</u> significantly increase the risk of mortality compared with no blood transfusion in the first 24 hours in patients with acute upper GI haemorrhage P=NR
EXTERNAL VALIDITY				
Generalisability				

The results of this study are generalisable to a population with acute severe gastrointestinal haemorrhage.
Applicability
The study was conducted in the UK so the results are likely to be applicable to the Australian setting.
Comments
The authors make no conclusions regarding mortality. The study is underpowered to detect a different in mortality between the two arms.

dL, decilitre; g, grams; GI, gastrointestinal; Hb, haemoglobin; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RCT, randomised controlled trial.

Level III evidence

STUDY DETAILS: Cohort study		
Citation		
Hearnshaw et al (2010) Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding. Alimentary Pharmacology and Therapeutics 32: 215–224.		
Affiliation/Source of funds		
John Radcliffe Hospital, Oxford, UK; University of Nottingham, Nottingham, UK; Western General Hospital, Edinburgh, UK. The study head was funded by NHS Blood and Transplant and the British Society of Gastroenterology. Representatives from both groups were involved in the design and reporting of the study. Hospitals did not receive financial support for the study.		
Study design	Level of evidence	Location/setting
Prospective cohort study	Level III-2	UK/hospital
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	Adjusted for: Rockall Index and baseline Hb	
Population characteristics (including size)		
Patients with acute upper GI bleeding, defined as haematemesis, the passage of melaena and/or firm clinical or laboratory evidence of acute blood loss from the upper GI tract. N=4441		
Length of follow-up	Outcomes measured	
30 days	30-day mortality	
Method of analysis		
Multivariable logistic regression used.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Hospital-based cohort study; 212/257 (82%) of hospitals participated; of 8939 potential submitted cases, 1199 did not meet exclusion criteria, 1190 had insufficient data, 5004 underwent endoscopy and 4441 had complete info on RBC transfusion; the authors note there were no important differences in demographic characteristics between those included and those excluded due to incomplete data; analysis adjusted for Rockall Score and baseline Hb; 30-day follow-up.		
RESULTS		
Population	With risk factor	Without risk factor

Available	6750			
Analysed	1974		2467	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
30-day mortality (N=4370)	RBC transfusion within 12 hours	No RBC transfusion within 12 hours	OR 1.28 (0.94, 1.74)	*RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in patients with acute upper GI haemorrhage* P=NR
30-day mortality In-patients only (N=722)	RBC transfusion within 12 hours	No RBC transfusion within 12 hours	OR 1.33 (0.83, 2.13)	*RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in in-patients with acute upper GI haemorrhage* P=NR
30-day mortality New-admission only (N=3596)	RBC transfusion within 12 hours	No RBC transfusion within 12 hours	OR 1.40 (0.92, 2.13)	*RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in newly admitted patients with acute upper GI haemorrhage* P=NR
30-day mortality Female (N=1714)	RBC transfusion within 12 hours	No RBC transfusion within 12 hours	OR 1.29 (0.82, 2.03)	*RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in females with acute upper GI haemorrhage* P=NR
30-day mortality Male (N=2727)	RBC transfusion within 12 hours	No RBC transfusion within 12 hours	OR 1.31 (0.86, 2.02)	*RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in males with acute upper GI haemorrhage* P=NR
30-day mortality Excluding patients with varices (N=4370)	RBC transfusion within 12 hours	No RBC transfusion within 12 hours	OR 1.26 (0.89, 1.79)	*RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in patients with acute upper GI haemorrhage excluding those with varices* P=NR

30-day mortality Excluding patients on aspirin (N=3036)	RBC transfusion within 12 hours	No RBC transfusion within 12 hours	OR 1.10 (0.75, 1.61)	*RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in patients with acute upper GI haemorrhage excluding those with aspirin* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population with acute upper GI haemorrhage.				
Applicability				
This study was conducted in the UK. The results of this study are likely applicable to the Australian setting.				
Comments				
The authors note that early RBC transfusion was associated with an increased risk of mortality but this didn't reach statistical significance. There is a possibility of residual confounding as only the Rockall Index and baseline haemoglobin was used. In a sub analysis excluding patients taking aspirin, the risk of mortality but substantially lower.				

CI, confidence interval; NHS, National Health Service; RBC, red blood cell; Hb, haemoglobin; GI, gastrointestinal; OR, odds ratio; NR, not reported.

F3 Evidence summary – Question 3

STUDY DETAILS: SR/MA		
Citation		
Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke MJ, Weingart O, Kluge S, Piper M, Napoli M, Rades D, Steensma D, Djulbegovic B, Fey MF, Ray-Coquard I,Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Engert A. (2009) Erythropoietin or Darbepoetin for patients with cancer - meta-analysis based on individual patient data. Cochrane Database of systematic reviews. Issue 3. Art. No.: CD007303. DOI: 10.1002/14651858.CD007303.pub2.		
Affiliation/Source of funds		
Julia Bohlius received honoraria and travel grants from Amgen. Andreas Engert received research funding and honoraria from Amgen, Roche and Johnson & Johnson. Gillian Thomas received research funding for the GOG-191 study by Johnson & Johnson. Benjamin Djulbegovic received research funding from OrthoBiotech and consulted for Amgen. Volker Moebus received research funding and honoraria from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, and Roche. Michael Untch received research funding for the PREPARE study from Amgen and Bristol-Myers Squibb. Margaret Piper ist employed by the Blue Cross and Blue Shield Association, the trade organization for the independent US Blue Cross Blue Shield health insurance plans, but is not involved in the determination of coverage and reimbursement policy for individual plans. All other members of the Steering Committee, the Statistical Analysis Team and Reviewers declared to have no conflict of interest.		
Study design	Level of evidence	Location/setting
Systematic review	I	International
Intervention	Comparator	
Cancer patients in the experimental group must have received short or long acting ESAs to prevent or reduce anemia, given singly or concomitantly with chemotherapy, radiotherapy, combination therapy or no therapy. ESAs had to be administered subcutaneously or intravenously. No minimum treatment duration or minimum ESA dosage was required for inclusion. Patients in both the control group and the experimental group(s) were to receive red blood cell transfusions if necessary. Supportive care such as iron given either as necessary or following a fixed schedule was allowed.	Placebo or no ESAs	
Population characteristics		
Pediatric and adult, male and female patients with a clinically or histologically confirmed diagnosis of cancer receiving or not receiving chemotherapy or radiotherapy or combined modality treatment were included. Both patients with solid and haematological malignancies were eligible. Studies on high-dose myeloablative chemotherapy regimens followed by bone marrow or peripheral blood stem cell transplantation, myelodysplastic syndromes or acute leukemia as well as trials using ESAs for short-term preoperative treatment were excluded. Studies were excluded if more than 20%of the entire patient population presents with an ineligible condition. However, if the respective study was randomized using a stratification technique and includes single strata that do fulfil the inclusion criteria, these strata were included in the analysis.		

Length of follow-up	Outcomes measured
NA	Overall survival, progression free survival, thromboembolic and cardiovascular events, need for transfusions and other safety and efficacy outcomes.

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating:

Description:

RESULTS

Outcome No. trials (No. patients)	ESA n/N (%) Mean ± SD (N)	Control n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
On study mortality 53 studies (N=13933)	865/7634 (11.3)	665/6299 (10.6)	HR 1.17 (95% CI 1.06, 1.30)[b]	*Favours control* P=0.0025 *No significant heterogeneity*[a] P=0.8735 (I^2=0)
	There was no evidence for heterogeneity between the trials (Isquare 0%, p=0.8735), for Forest plot see Figure 6, for pooled Kaplan-Meier curve see Appendix 4. There was no evidence for small study effects: linear regression test p=0.1371, rank correlation test of funnel plot asymmetry p=0.9588. For Funnel plot see Figure 7. Two studies contributed more than 10% weight to the overall analysis (Leyland-Jones 2003; Smith 2008). In the study published by Leyland-Jones 2003 (study number 17100) 937 patients with metastatic cancer undergoing chemotherapy received ESA or placebo for 52 weeks, therefore the study has a much longer on study phase compared to other studies. In the study published by Smith et al 2008 (study number 81215) 989 patients were treated with ESA without concomitant myelosuppressive chemotherapy. The impact of single studies was assessed in an influence analysis, see Figure 8. When excluding study 17100 (Leyland-Jones 2003), the overall HR slightly decreased and the confidence interval still excluded 1. Exclusion of any of the other studies did not markedly change the overall estimate.			
Median (IQR) follow-up (on study mortality), months 53 studies (N=13933)	3.71 (2.8 to 5.1)	3.94 (2.9 to 5.3)	NA	NA

Bivariate analyses for on study mortality in all cancer patients

The authors presented adjusted HRs adjusted individually for all of the following variables: hb at baseline, tumour category, sex, age, hct, baseline serum EPO, ECOG score, BMI, history of thromboembolic events, history of cardiovascular events, history of hypertension, history of diabetes melitis, geographic region, metastasis, time from cancer diagnosis to randomisation. The adjusted HRs did not differ substantially from the unadjusted HR for any of these variables.

Therefore the bivariate analyses do not support the hypothesis that baseline imbalances of prognostic factors analysed influenced the overall results.

Multivariate analysis of on study mortality in all cancer patients				
Model 1 (includes age, sex, Hb at baseline and tumour type)	NR	NR	Unadjusted HR 1.17 (1.06, 1.30) Adjusted HR 1.17 (1.06, 1.30)	
Model 2 (includes age, sex, Hb at baseline, tumour type, underlying tumour)	NR	NR	Unadjusted HR 1.22 (1.09, 1.36) Adjusted HR 1.21 (1.08, 1.35)	
Model 3 (includes age, sex, Hb at baseline, tumour type, BMI, region)	NR	NR	Unadjusted HR 1.16 (1.03, 1.30) Adjusted HR 1.16 (1.03, 1.30)	
Model 4 (includes age, sex, Hb at baseline, tumour type, BMI, region, ECOG, haematocrit)	NR	NR	Unadjusted HR 1.23 (1.08, 1.39) Adjusted 1.20 (1.06, 1.37)	
Objective 2 for on study mortality: is there a specific subgroup of patients that is at increased or decreased risk to die when receiving ESAs compared to controls? Three variables (planned frequency of ESA administration, history of thromboembolic events, haematocrit) showed a statistically significant (P<0.1) interaction with ESAs on mortality in the bivariate analyses and were included in the multivariate model (model 1). This model included the variables age, sex, Hb at baseline, and tumour category. Multivariate analyses suggested the following: • Effect modification of hct at baseline can only to a certain extent be explained by confounding with other patient characteristics (hb, age, sex, tumour type). However, because of large amounts of missing data uncertainty remains • Effect modification of history of thromboembolic events was robust in sensitivity analyses for additional patient characteristics (hb, age, sex, tumour type); [uncertainty still remains) • Effect modification for planned frequency of ESA application is likely to be confounded by other study design aspects.				
On study mortality (chemotherapy trials[c]) 38 studies (N=10441)	605/5676 (10.7)	490/4765 (10.3)	HR 1.10 (0.98, 1.24)	*Favours control* P=0.7152 *No significant heterogeneity[a]* P=0.7152 (I^2=0)

Median (IQR) follow-up (on study mortality in chemotherapy trials[c]), months	4.1 (3.0 to 5.6)	4.3 (3.4 to 5.7)		
There was no evidence for small study effects: linear regression test p=0.1743, rank correlation test of funnel plot asymmetry p=0.7437. One study contributed 19.9% weight to the overall analysis (Leyland-Jones 2003). In this study 937 patients with metastatic cancer undergoing chemotherapy received ESA or placebo for 52 weeks, therefore the study has a much longer on study phase compared to the other studies. Excluding this study decreased the overall HR (1.03 [95% CI 0.90, 1.18]). The margins of the confidence intervals were not influenced by exclusion of any of the other studies.				
Bivariate analysis for on study mortality in chemotherapy trials[c] The authors presented adjusted HRs adjusted individually for all of the following variables: hb at baseline, tumour category, sex, age, hct, baseline serum EPO, ECOG score, BMI, history of thromboembolic events, history of cardiovascular events, history of hypertension, history of diabetes melitis, geographic region, metastasis, time from cancer diagnosis to randomisation. The adjusted HRs did not differ substantially from the unadjusted HR for any of these variables. Therefore the bivariate analyses do not support the hypothesis that baseline imbalances of prognostic factors analysed influenced the overall results.				
Multivariate analysis for on study mortality in chemotherapy trials[c]				
Model 1 (includes age, sex, hb at baseline, tumour type)	NR	NR	Unadjusted 1.10 (0.98, 1.25) Adjusted 1.12 (0.99, 1.26)	
Model 2 (includes age, sex, hb at baseline, tumour type, tumour stage)	NR	NR	Unadjusted 1.16 (1.02, 1.33) Adjusted 1.17 (1.02, 1.33)	
Model 3 (includes age sex, hb at baseline, tumour type, BMI)	NR	NR	Unadjusted 1.07 (0.94, 1.23) Adjusted 1.08 (0.95, 1.24)	
Model 4 (includes age, sex, hb at baseline, tumour type, BMI, ECOG, haematocrit)	NR	NR	Unadjusted 1.13 (0.97, 1.31) Adjusted 1.16 (0.99, 1.34)	Therefore: available evidence does not support the hypothesis that baseline imbalances of prognostic factors analysed influenced the overall results.

Objective 2 for on study mortality (chemotherapy trials): is there a specific subgroup of patients that is at increased or decreased risk to die when receiving ESAs compared to controls (chemotherapy trials[c])? Two variables (concealment of allocation, planned frequency of ESA administration) showed a statistically significant (P<0.1) interaction with ESAs on mortality in the bivariate analysis and were included in the multivariate model. This model included the variables age, sex, Hb at baseline, and tumour category. Adjusting for these parameters did not markedly influence the effect estimates and the P values for interaction. [ie, multivariate analysis did not markedly effect the P values for interaction]. For both of the two variables the interaction was borderline significant (P=0.0722 for concealment of allocation and P=0.0544 for planned frequency of ESA administration) Overall, there is no strong evidence to support the hypothesis that ESAs had different effects in sub-populations that differed for the variables tested in the chemotherapy population.				
Overall survival (all cancer patients) 53 studies (N=13933)	2643/7634 (34.6)	2350/6299 (37.3)	HR 1.06 (1.00, 1.12)	*Favours control* P=0.3288 *No significant heterogeneity[a]* P=0.3288 (I^2=7.1)
Median (IQR) follow-up, months	6.2 (3.2 to 15.4)	8.3 (3.7 to 19.6)	NR	NR
There was no evidence for small study effects: linear regression test p=0.7567, rank correlation test of funnel plot asymmetry p=0.602. Two studies contributed 9.5% and 10.1% weight to the overall analysis (Pirker 2008), (Smith 2008). In the study published by Smith 2008) (study number 81215) 989 patients were treated with ESA or placebo without concomitant myelosuppressive chemotherapy. In the study published by (Pirker 2008) (study number 89335) 600 patients with untreated, extensive SCLC underwent chemotherapy and were randomized to receive ESA or placebo. The influence of single studies was assessed; see Figure 14, exclusion of single studies at a time did not influence the overall result.				
Bivariate analysis for overall survival in cancer patients The authors presented adjusted HRs adjusted individually for all of the following variables: hb at baseline, tumour category, sex, age, hct, baseline serum EPO, ECOG score, BMI, history of thromboembolic events, history of cardiovascular events, history of hypertension, history of diabetes melitis, geographic region, metastasis, time from cancer diagnosis to randomisation. The adjusted HRs did not differ substantially from the unadjusted HR for any of these variables. Therefore the bivariate analyses do not support the hypothesis that baseline imbalances of prognostic factors analysed influenced the overall results.				
Multivariate analysis for overall survival in cancer patients				
Model 1 (includes age, sex, hb at baseline, tumour type)	NR	NR	<u>Unadjusted</u> HR 1.06 (1.00, 1.12) <u>Adjusted</u> HR 1.06 (1.00, 1.12)	

Model 2 (includes age, sex, hb at baseline, tumour type, tumour stage)	NR	NR	Unadjusted HR 1.06 (1.00, 1.13) Adjusted HR 1.05 (1.00, 1.12)	
Model 3 (includes age sex, hb at baseline, tumour type, BMI)	NR	NR	Unadjusted HR 1.04 (0.98, 1.11) Adjusted HR 1.04 (0.98, 1.11)	
Model 4 (includes age, sex, hb at baseline, tumour type, BMI, ECOG, haematocrit)	NR	NR	Unadjusted HR 1.07 (0.99, 1.15) Adjusted HR 1.09 (1.01, 1.17)	
Objective 2 for overall survival: is there a specific subgroup of patients that is at increased or decreased risk to die when receiving ESAs compared to controls? Two variables (planned frequency, hct at baseline) showed a statistically significant (p<0.1) interaction term in the bivariate analysis and was included in the multivariate model. Multivariate adjustments did not markedly effect the estimates; however, corresponding P values for interaction did not reach conventional levels of significance. Overall, available evidence does not support the hypothesis that ESAs had different effects in sub-populations that differed for any of the variables tested for overall survival in all cancer patients.				
Overall survival (chemotherapy trials[c]) 38 studies (N=10441)	1888/5676 (33.3)	1667/4765 (35.0)	HR 1.04 (0.97, 1.11)	*Favours control* P=0.3775 *No significant heterogeneity[a]* P=0.3775 (I^2=5.3)
Median (IQR) follow up for overall survival (chemotherapy trials), months	6.7 (3.4 to 15.7)	8.4 (3.7 to 19.1)	NR	NR
There was no evidence for small study effects: linear regression test p=0.7008, rank correlation test of funnel plot asymmetry p=0.6782. One study contributed about 14% weight to the overall analysis (Pirker 2008). In this study (Pirker 2008) (study number 89335) 600 patients with untreated, extensive SCLC underwent chemotherapy and were randomized to receive ESA or placebo. Exclusion of single studies at a time did only marginally influence the overall results.				

Bivariate analysis for overall survival in chemotherapy trials The authors presented adjusted HRs adjusted individually for all of the following variables: hb at baseline, tumour category, sex, age, hct, baseline serum EPO, ECOG score, BMI, history of thromboembolic events, history of cardiovascular events, history of hypertension, history of diabetes melitis, geographic region, metastasis, time from cancer diagnosis to randomisation. The adjusted HRs did not differ substantially from the unadjusted HR for any of these variables. Therefore the bivariate analyses do not support the hypothesis that baseline imbalances of prognostic factors analysed influenced the overall results in chemotherapy trials.				
Model 1 (includes age, sex, hb at baseline, tumour type)	NR	NR	<u>Unadjusted</u> HR 1.04 (0.97, 1.11) <u>Adjusted</u> HR 1.05 (0.98, 1.12)	
Model 2 (includes age, sex, hb at baseline, tumour type, tumour stage)	NR	NR	<u>Unadjusted</u> HR 1.05 (0.98, 1.13) <u>Adjusted</u> HR 1.05 (0.98, 1.13)	
Model 3 (includes age sex, hb at baseline, tumour type, BMI)	NR	NR	<u>Unadjusted</u> HR 1.01 (0.94, 1.09) <u>Adjusted</u> HR 1.02 (0.94, 1.10)	
Model 4 (includes age, sex, hb at baseline, tumour type, BMI, ECOG, haematocrit)	NR	NR	<u>Unadjusted</u> HR 1.02 (0.94, 1.11) <u>Adjusted</u> HR 1.04 (0.96, 1.14)	
Objective 2 for overall survival (chemotherapy trials): is there a specific subgroup of patients that is at increased or decreased risk to die when receiving ESAs compared to controls? One variable (sex) showed a statistically significant ($p<0.1$) interaction term in the bivariate analysis and was included in the multivariate model. Within the chemotherapy population there was no convincing evidence to support the hypothesis that ESAs had different effects in sub-populations that differed for any of the variables tested. However, effect modification of sex cannot be explained by confounding with other patient characteristics (hb, age, sex, tumour type).				
Mortality within 12 months (on study survival for radiotherapy trials)	NR	NR	HR 1.51 (0.97, 2.35) 82 deaths	*Favours control* P=0.067
Mortality within 12 months (overall survival for radiotherapy trials)	NR	NR	HR 1.12 (0.93, 1.36) 441 deaths	*Favours control* P=0.219

Mortality within 60 months (overall survival for radiotherapy trials)	NR	NR	HR 1.03 (0.90, 1.19) 825 deaths	*Favours control* P=0.631
Mortality within 12 months (on study survival for trials without concomitant radiotherapy and/or chemotherapy)	NR	NR	HR 1.37 (1.06, 1.78) 230 deaths	*Favours control* P=0.018
Mortality within 12 months (overall survival for trials without concomitant radiotherapy and/or chemotherapy)	NR	NR	HR 1.27 (1.05, 1.54) 430 deaths	*Favours control* P=0.013
Mortality within 36 months (overall survival for trials without concomitant radiotherapy and/or chemotherapy)	NR	NR	HR 1.22 (1.02, 1.47) 466 deaths	*Favours control* P=0.032
EXTERNAL VALIDITY				
Generalisability				
Applicability				
Comments				
Note: mortality for chemotherapy was comparable with that of the other treatment group There is a need to for individuals patient data meta-analysis for quality of life.				

STUDY DETAILS: SR/MA
Citation
CADTH 2009 Tonelli M, Lloyd A, Lee H, Wiebe N, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Klarenbach S. (2009) Erythropoiesis-stimulating agents for anemia of cancer or of chemotherapy: systematic review and economic evaluation [Technology report number 119]. Ottawa: Canadian Agency for Drugs and Technologies in Health.
Affiliation/Source of funds
Marcello Tonelli, Scott Klarenbach, Brenda Hemmelgarn, and Braden Manns received an unrestricted grant award to the Alberta Kidney Disease Network from Amgen Inc., and Amgen Inc. is not entitled to the results prior to publication and did not dictate the content or focus of the work. Tony Reiman has been an investigator on a number of clinical trials of erythropoietic agents for cancer patients and, although the centre did receive payment for work done by clinical trial nurses and study coordinators on a contractual basis, no direct payment was received for this work. All other authors declared no other conflicts of interest. Douglas Stewart has received honoraria for advisory boards and talks and research funding from Hoffmann-La Roche Ltd.

Study design	Level of evidence	Location/setting
SR	I	NA

Intervention	Comparator
ESAs	No ESAs
Population characteristics	
Adult patients with anaemia that is due to cancer or chemotherapy	
Length of follow-up	Outcomes measured
NA	Mortality (all-cause), cardiovascular events (MI, stroke, congestive heart failure, revascularization), hospitalisation (all cause, cardiovascular), QoL (anemia, fatigue, general domains from the FACT), red cell transfusion, hypertension, and adverse events.
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Good Description: 52 included studies (at least 5 good quality)	
RESULTS	

Outcome No. trials (No. patients)	ESAs n/N (%) Mean ± SD (N)	No ESAs n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
On study mortality 31 trials (N=6525)	515/3789 (13.6)	360/2736 (13.2)	RR 1.15 (1.03, 1.29)	*Favours no ESAs* P=0.01 *No significant heterogeneity*[a] P=0.63 (I^2=0)
On study mortality (epoetin vs none) 24 trials (N=3744)	291/2163 (13.5)	207/1581 (13.1)	RR 1.12 (0.97, 1.29)	*Favours no ESAs* P=0.13 *No significant heterogeneity*[a] P=0.58 (I^2=0)
On study mortality (darbepoetin vs none) 7 trials (N=2781)	224/1626 (13.8)	153/1155 (13.2)	RR 1.12 (1.01, 1.47)	*Favours no ESAs* P=0.01 *No significant heterogeneity*[a] P=0.50 (I^2=0)
On study mortality (darbepoetin vs epoetin) 2 trials (N=1567)	101/791 (12.8)	109/776 (14.0)	RR 0.99 (0.58, 1.69)	*Favours darbepoetin* P=0.98 *Substantial heterogeneity*[a] P=0.06 (I^2=72.4)

Mortality including post-treatment follow-up [median 12 months] 16 trials (N=5075)	1478/2728 (54.2)	1280/2347 (54.5)	RR 1.01 (0.96, 1.07)	*Favours no ESAs* P=0.66 *Moderate heterogeneity*[a] P=0.08 (I^2=34.7)
Mortality including post-treatment follow-up (epoetin vs none) 11 trials (N=2447)	693/1341 (51.7)	547/1106 (49.5)	RR 1.01 (0.95, 1.07)	*Favours no ESAs* P=0.68 *No significant heterogeneity*[a] P=0.59 (I^2=0)
Mortality including post-treatment follow-up (darbepoetin vs none) 5 trials (N=2628)	785/1387 (56.6)	733/1241 (59.1)	RR 1.02 (0.89, 1.16)	*Favours no ESAs* P=0.79 *Substantial heterogeneity*[a] P=0.004 (I^2=73.8)
Cardiovascular events 16 trials (N=3281)	104/1839 (5.7)	74/1442 (5.1)	RR 1.12 (0.83, 1.50)	*Favours no ESAs* P=0.47 *No significant heterogeneity*[a] P=0.90 (I^2=0)
Cardiovascular events (epoetin vs none) 14 trials (N=2078)	56/1160 (4.8)	38/918 (4.1)	RR 1.22 (0.80, 1.84)	*Favours no ESAs* P=0.36 *No significant heterogeneity*[a] P=0.36 (I^2=0)
Cardiovascular events (darbepoetin vs none) 2 trials (N=1203)	48/679 (7.1)	36/524 (6.9)	RR 1.02 (0.67, 1.56)	*Favours no ESAs* P=0.92 *No significant heterogeneity*[a] P=0.95 (I^2=0)
Change in LASA [Linear Analog Scale Assessment] 7 trials (N=1326)	NR	NR	WMD 12.24 (6.29, 18.19)	*Favours ESAs* P<0.0001 *Substantial heterogeneity*[a] P<0.0001 (I^2=80.6)
Change in FACT-anaemia (total) [Functional Assessment of Cancer Therapy] 3 trials (N=526)	NR	NR	WMD 14.66 (-1.09, 30.411)	*Favours ESAs* P=0.07 *Substantial heterogeneity*[a] P<0.00001 (I^2=93.1)

Change in FACT-anaemia (general) 3 trials (N=709)	NR	NR	WMD 4.11 (2.00, 6.22)	*Favours ESAs* P=0.0001 *No significant heterogeneity*[a] P=0.55 (I^2=0)
Change in FACT-Fatigue subscale 10 trials (N=3169)	NR	NR	WMD 3.00 (1.36, 4.64)	*Favours ESAs* P=0.0004 *Substantial heterogeneity*[a] P=0.0001 (I^2=72.9)
Change in FACT-Fatigue subscale (darbepoetin vs epoetin) 4 trials (N=830)	NR	NR	WMD 2.19 (-1.23, 5.62)	*Favours darbepoetin* P=0.21 *No significant heterogeneity*[a] P=0.32 (I^2=14.2)
Change in FACT-Fatigue subscale (epoetin vs none) 6 trials (N=1423)	NR	NR	RR 4.57 (3.32, 5.81)	*Favours ESAs* P<0.0001 *No significant heterogeneity*[a] P=0.63 (I^2=0)
Change in FACT-Fatigue subscale (darbepoetin vs none) 4 trials (N=1746)	NR	NR	RR 0.80 (-0.92, 2.51)	*Favours ESAs* P=0.36 *Substantial heterogeneity*[a] P=0.09 (I^2=54.6)
Change in FACT-Anemia subscale 7 trials (N=1420)	NR	NR	RR 3.90 (1.63, 6.16)	*Favours ESAs* P=0.0008 *Substnatial heterogeneity*[a] P<0.0001 (I^2=83.6)
Red cell transfusion incidence 31 trials (N=5321)	707/2882 (24.5)	952/2439 (39.0)	RR 0.64 (0.56, 0.73)	*Favours ESAs* P<0.0001 *Substantial heterogeneity*[a] P=0.0001 (I^2=55.3)
Red cell transfusion incidence (epoetin vs none) 28 trials (N=4121)	579/2229 (26.0)	739/1892 (39.1)	RR 0.65 (0.56, 0.75)	*Favours ESAs* P<0.0001 *Substantial heterogeneity*[a] P=0.0004 (I^2=53.8)

Red cell transfusion incidence (darbepoetin vs none) 3 trials (N=1200)	128/653 (19.6)	213/547 (38.9)	RR 0.58 (0.41, 0.83)	*Favours ESAs* P=0.003 *Substantial heterogeneity*[a] P=0.07 (I^2=61.6)
Red cell transfusion incidence (patients with solid tumour) 18 trials (N=858)	371/1541 (24.1)	487/1306 (37.3)	RR 0.61 (0.51, 0.74)	*Favours ESAs* P<0.0001 *Substantial heterogeneity*[a] P=0.002 (I^2=56.3)
Red cell transfusion incidence (patients with haematological cancer) 5 trials (N=489)	71/287 (24.7)	55/202 (27.2)	RR 0.97 (0.72, 1.32)	*Favours ESAs* P=0.87 *No significant heterogeneity*[a] P=0.81 (I^2=0)
Red cell transfusion incidence (trials with mixed cancer types) 4 trials (N=658)	130/339 (38.3)	165/319 (51.7)	RR 0.74 (0.63, 0.88)	*Favours ESAs* P=0.0005 *No significant heterogeneity*[a] P=0.52 (I^2=48.1)
Red cell transfusions (week 5 to EOS) 21 trials (N=3552)	467/2180 (21.4)	571/1372 (41.6)	RR 0.57 (0.52, 0.63)	*Favours ESAs* P<0.0001 *No significant heterogeneity*[a] P=0.50 (I^2=0)
Red cell transfusions (week 5 to EOS; epoetin vs none) 10 trials (N=1839)	254/1118 (22.7)	300/721 (41.6)	RR 0.55 (0.46, 0.66)	*Favours ESAs* P<0.0001 *Moderate heterogeneity*[a] P=0.07 (I^2=42.9)
Red cell transfusions (week 5 to EOS; darbepoetin vs none) 11 trials (N=1713)	213/1062 (20.1)	271/651 (41.6)	RR 0.57 (0.49, 0.66)	*Favours ESAs* P<0.0001 *No significant heterogeneity*[a] P=0.93 (I^2=0)
Red cell transfusions (week 5 to EOS; epoetin vs darbepoetin) 6 trials (N=1676)	174/888 (19.6)	127/788 (16.1)	RR 0.84 (0.50, 1.40)	*Favours darbepoetin* P=0.49 *Substantial heterogeneity*[a] P=0.03 (I^2=59.2)

Transfusion volume, units 20 trials (N=2563)	NR	NR	RR -0.80 (-0.99, -0.61)	*Favours ESAs* P<0.0001 *No significant heterogeneity*[a] P=0.30 (I^2=12.4)
Transfusion volume (epoetin vs none), units 19 trials (N=2266)	NR	NR	RR -0.77 (-0.95, -0.58)	*Favours ESAs* P<0.0001 *No significant heterogeneity*[a] P=0.36 (I^2=8.0)
Transfusion volume (darbepoetin vs none), units 1 trial (N=297)	0.67 (1.70)	1.92 (3.27)	RR -1.25 (-1.84, -0.66)	*Favours ESAs* P<0.0001
SAEs 23 trials (N=5891)	1123/3307 (34.0)	787/2584 (30.5)	RR 1.16 (1.08, 1.25)	*Favours no ESAs* P<0.0001 *No significant heterogeneity*[a] P=0.74 (I^2=0)
SAEs (epoetin vs none) 18 trials (N=3421)	545/1911 (28.5)	374/1510 (24.8)	RR 1.17 (1.05, 1.30)	*Favours no ESAs* P=0.004 *No significant heterogeneity*[a] P=0.71 (I^2=0)
SAEs (darbepoetin vs none) 5 trials (N=2470)	578/1396 (41.4)	413/1074 (38.5)	RR 1.15 (1.04, 1.27)	*Favours no ESAs* P=0.005 *No significant heterogeneity*[a] P=0.41 (I^2=0)
Thrombotic events 14 trials (N=3420)	138/1876 (7.4)	68/1544 (4.4)	RR 1.69 (1.27, 2.24)	*Favours no ESAs* P=0.00003 *No significant heterogeneity*[a] P=0.95 (I^2=0)
Thrombotic events (epoetin vs none) 12 trials (N=2510)	104/1422 (7.3)	48/1088 (4.4)	RR 1.68 (1.20, 2.35)	*Favours no ESAs* P=0.002 *No significant heterogeneity*[a] P=0.89 (I^2=0)
Thrombotic events (darbepoetin vs none) 2 trials (N=910)	34/454 (7.5)	20/456 (4.4)	RR 1.71 (1.00, 2.92)	*Favours no ESAs* P=0.05 *No significant heterogeneity*[a] P=0.72 (I^2=0)

Thrombotic events (darbepoetin vs epoetin) 3 trials (N=1702)	49/860 (5.7)	61/842 (7.2)	RR 0.79 (0.55, 1.13)	*Favours darbepoetin* P=0.20 *No significant heterogeneity*[a] P=0.44 (I^2=0)
EXTERNAL VALIDITY				
Generalisability				
The review is generalisable to cancer patients with anaemia				
Applicability				
Applicable to the Australian context.				
Comments				

STUDY DETAILS: RCT		
Citation		
Christodoulou C, Dafni U, Aravantinos G, Koutras A, Samantas E, Karina M, Janinis J, Papakostas P, Skarlos D, Kalofonos HP, Fountzilas G (2009) Effects of epoetin-(alpha) on quality of life of cancer patients with solid tumors receiving chemotherapy. Anticancer Res 29(2):693–702.		
Affiliation/Source of funds		
Metropolitan Hospital, Athens; University of Athens; University of Patras; Agii Anargiri Cancer Hospital Athens; University of Thessaloniki; Social Security Organisation Oncology Centre Athens; Ippokration Hospital Athens.		
Study design	Level of evidence	Location/setting
RCT, open label	Level II	Multiple centres, Greece
Intervention	Comparator	
EPO-α 10,000IU thrice weekly subcut	No treatment	
Population characteristics		
337 adult patients with solid tumours, Hb ≤12 g/dL, concurrent chemotherapy (not high-dose), performance status ≤2 (WHO), life expectancy at least 3 months. All patients received daily 200mg elemental iron.		
Length of follow-up	Outcomes measured	
median 14.3 months	QOL, transfusion requirement, anaemia	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Quality rating: Poor The study was an open label RCT with a primary outcome of QOL. The open-label nature of the trial may have affected the QOL results. The analysis of the primary outcome of QOL was poor (not a correct ITT or PP analysis) and did not allow any of the data for QOL to be extracted.		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	399	

Efficacy analysis (ITT)				
Efficacy analysis (PP)	167		170	
Safety analysis	NA		NA	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Patients requiring transfusion	16/167	36/170		P=0.0035
No units transfused per patient	0.24	0.61		P=0.003
Overall survival (months)	10.39	14.59		P=0.16
EXTERNAL VALIDITY				
Generalisability				
The results of the study are generalisable to a population of adult patients with solid tumours, who are anaemic.				
Applicability				
The study was performed at multiple centres in Greece. The results are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that transfusion incidence and volume are both significantly lower in patients treated with EPO.				

STUDY DETAILS: RCT		
Citation		
Hernandez E, Ganly P, Charu V, DiBenedetto J, Tomita D, Lilliee T, Taylor K (2009) Randomized, double-blind, placebo-controlled trial of every-3-week darbepoetin alfa 300 micrograms for treatment of chemotherapy-induced anemia. Curr Med Res Opin 25(9):2109–20.		
Affiliation/Source of funds		
Funding: Amgen Inc. Affiliations: Temple University Hospital, Pennsylvania, PA USA; Canterbury Health Laboratories, Christchurch, New Zealand; Pacific Cancer Medical Centre, Anaheim, CA, USA; Oncology Hematology Associates, Providence, RI, USA; Amgen, Thousand Oaks, CA, USA; Mater Medical Centre, South Brisbane, QLD, Australia.		
Study design	Level of evidence	Location/setting
RCT, double-blinded	Level II	81 sites in Australia, New Zealand and North America
Intervention	Comparator	
Darbopoetin 300µg subcut every 3 weeks	Placebo injection	
Population characteristics		

Adult patients with non-myeloid malignancy, Hb <11 g/dL, scheduled for ≥12 weeks of chemotherapy. Patients with uncontrolled hypertension, iron deficiency, 2 RBC transfusions in the previous 4 weeks, any RBC transfusion in the previous 4 weeks, planned RBC transfusions after randomisation, or EPO therapy in the previous 4 weeks or planned after randomisation were excluded. Iron therapy was recommended if : seum iron <500 μg/L, serum ferritin <10 ng/mL, transferring saturation <20%				
Length of follow-up		Outcomes measured		
19 weeks		Transfusion incidence, transfusion volume, QOL		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Quality rating: Fair The study is a double-blinded placebo controlled RCT. The method of analysis used for transfusion incidence was unusual. Reporting of randomisation and allocation concealment was poor and the length of follow up was short.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	196		195	
Efficacy analysis (ITT)	193		193	
Efficacy analysis (PP)	138		132	
Safety analysis	194		192	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Transfusion incicdence (week 5 to end, adjusted Kaplan-Meier estimate)	24% N=181	41% N=185	Mean difference: -16.3% (-25.9, -6.6)	P<0.001
Transfusion incicdence (week 1 to end, adjusted Kaplan-Meier estimate)	30% N=193	47% N=193	Mean difference: -14.6% (-31.29, -4.6)	P=0.003
FACT-F	Change from baseline <3		NR	NR
All-cause mortality	17/194	20/192	NR	NR
Embolism/thrombosis (arterial and venous)	16/194	11/192	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to an adult population with non-myeloid malignancy and anaemia				
Applicability				

The study was carried out at multiple centres in Australia, New Zealand and North America. The results of the study are directly applicable to the Australian setting.
Comments
The authors conclude that darbopoetin treatment reduces transfusion incidence but does not significantly affect QOL.

STUDY DETAILS: RCT		
Citation		
Hoskin PJ, Robinson M, Slevin N, Morgan D, Harrington K, Gaffney C (2009) Effect of epoetin alfa on survival and cancer treatment-related anemia and fatigue in patients receiving radical radiotherapy with curative intent for head and neck cancer. J Clin Oncol 27(34):5751–6.		
Affiliation/Source of funds		
Funding Johnson & Johnson Pharmaceutical Research and Development Affiliation: Mount Vernon Cancer Centre, Northwood; Sheffield Teaching Hospitals National Health Service (NHS) Foundation Trust and Sheffield University Cancer Research Centre, Weston Park Hospital, Sheffield; Christie Hospital NHS Foundation Trust, Christie Hospital and Holt Radium Institute, Manchester; Nottingham University Hospitals NHS Trust, City Hospital Campus, Nottingham; Royal Marsden NHS Foundation Trust, Royal Marsden Hospital, London; and Velindre NHS Trust, Velindre Hospital, Cardiff, United Kingdom.		
Study design	Level of evidence	Location/setting
RCT, open label	Level II	21 sites in the United Kingdom

Intervention	Comparator
EPO-α 10,000IUsubcut 3 times weekly until Hb was more than 12.5 g/dL. When Hb reached 12.5 g/dL, dosage was reduced to 4,000 U SC three times weekly. Oral iron 200mg per day.	No treatment and oral iron 200mg per day.

Population characteristics
Adult patients with histologically confirmed squamous cell cancer of the head and neck for which radical radiotherapy with curative intent (any regimen designed for long-term local tumor control within the irradiation volume) was scheduled. Any planned postoperative radiotherapy was to begin 6 to 12 weeks postoperatively. Patients were required to have stage I-III (excluding stage I tumors of the glottic larynx) malignancy, life expectancy6 months, and Hb less than 15 g/dL at entry. Excluded patients had secondary metastases (other than regional nodal disease); history of other cancer (except basal cell carcinoma); previous chemotherapy for their existing head and neck cancer; accelerated radiotherapy schedules with an overall treatment time less than 4 weeks or less than 3 weeks with less than 3 weeks available before radiotherapy, or using more than once daily fractionation; clinically significant disease/dysfunction; poorly controlled hypertension; chronic inflammatory conditions; acute major illness within 7 days of entry; surgery, transfusion, or major infection within 28 days of entry; or surgery under general anesthesia within 7 days of entry. **The majority of patients (78%) had Hb ≥12.5 g/dL at baseline, they may not count as anaemic.**

Length of follow-up	Outcomes measured
Up to 5 years	Local disease-free survival, overall survival (at 1, 2 and 5 years), change from baseline in anaemia and fatigue.

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Quality rating: Poor The reporting of randomisation was incomplete. Possible bias in QOL reporting due to open label status.

RESULTS		
Population analysed	Intervention	Comparator
Randomised	302	

Efficacy analysis (ITT)	151		149	
Efficacy analysis (PP)				
Safety analysis	133		149	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Overall survival (median, months)	56.67 (33.35, NA)	58.64 (37.95, NA)		P=0.823
FACT-G total score (mean change form baseline)	-1.2 (13.19)	-2.4 (13.78)		P=0.509
Physical well-being	-1.1 (5.32)	-1.5 (5.55)		P=0.500
Social/Family well-being	0.1 (3.93)	-0.6 (3.64)		P=0.097
Emotional well-being	1.3 (3.90)	1.3 (3.87)		P=00.994
Functional well-being	-1.2 (5.93)	-1.7 (5.79)		P=0.471
FACT-Anaemia total score (mean change form baseline)	-3.3 (26.41)	-5.2 (27.43)		P=0.915
Total fatigue	-2.6 (10.67)	-2.6 (12.45)		P=0.966
Total non-fatigue	-0.5 (3.68)	-1.0 (4.00)		P=0.299
FACT-fatigue total score (mean change form baseline)	-3.1 (22.88)	-4.4 (24.81)		P=0.982
FACT-head&neck	-2.5 (7.66)	-3.4 (7.17)		P=0.318
Total FACT-head&neck	-4.6 (19.69)	-6.4 (18.82		P=0.475
Thromboembolic events (stroke/MI/DVT/PE) [a]	2/133	0/149		NR
Mortality	53%	50%		NR
EXTERNAL VALIDITY				
Generalisability				
The results of the study are generalisable to a population of adult head and neck cancer patients with anaemia.				
Applicability				
The study was carried out at multiple centres in the United Kingdom. The results of the study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that EPO treatment had no effect on overall survival or quality of life.				

STUDY DETAILS: RCT		
Citation		
Pronzato P, Cortesi E, van der Rijt CC, Bols A, Moreno-Nogueira JA, de Oliveira CF, Barrett-Lee P, Ostler PJ, Rosso R (2010) Epoetin alfa improves anemia and anemia-related, patient-reported outcomes in patients with breast cancer receiving myelotoxic chemotherapy: Results of a european, multicenter, randomized, controlled trial. Oncologist 15(9):935–43.		
Affiliation/Source of funds		
Funding: Johnson& Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ. Affliiations: Oncologia Medica, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy; Università degli Studi, Rome, Italy; Erasmus MC, Daniel den Hoed Oncological Center, Rotterdam, The Netherlands; A.Z. St. Jan, Brugge, Belgium; Servicio de Oncologia, Hospital Virgen del Rocio, Seville, Spain; Hospitais da Universidade de Coimbra, Coimbra, Portugal; Academic Breast Oncology Unit, Velindre Hosp, Cardiff, United Kingdom; Department of Oncology, Mount Vernon Hospital, Northwood, Luton, United Kingdom; Scientific Direction, National Institute for Cancer Research, Genova, Italy.		
Study design	Level of evidence	Location/setting
RCT, open label	Level II	Multiple sites in Italy, Spain, Portugal, Belgium, The Netherlands and the United Kingdom.
Intervention	Comparator	
EPO-α 10,000IU subcut 3 times weekly until 4 weeks afer their last chemotherapy cycle.	Best standard care	
Population characteristics		
Adult female patients with breast cancer, Hb ≤12 g/dL, receiving myelotoxic chemotherapy for a planned minimum of 12 weeks, Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–3, a life expectancy 6 months, and adequate renal, hepatic, and hematologic function (not the result of transfusion).		
Length of follow-up	Outcomes measured	
1 year after last study assessment.	QOL (FACT-An and CLAS); hematologic response; scores on the fatigue and nonfatigue subscales of the FACT-An; scores for CLAS energy, ability to do daily activities, and overall quality of life; ECOG PS score; tumor response to chemotherapy; and 6-month and 12-month overall survival rates.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Quality rating: Fair Randomisation method not reported. Possibility for bias in the reporting of QOL outcomes with the open label design.		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	223	
Efficacy analysis (ITT)	107	109
Efficacy analysis (PP)	84	91
Safety analysis		

Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Total FACT-An (% mean change from baseline)	14.2% N=70	-0.5% N=71		P=0.002
Fatigue subscale	17.5% N=70	-0.9% N=71		P=0.003
Non-fatigue subscale	8.8% N=70	0.2% N=71		P=0.008
Transfusion incidence	8/107 (7.5%)	18/109 (165%)		P=0.059
Mortality	23/110 (20.9%)	20/113 (17.7%)		NS
Venous thrombosis	8/109 (7.3%)	7/111 (6.3%)		
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of adult female breast cancer patients with anaemia.				
Applicability				
The study was conducted in multiple European centres. The results are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that EPO treatment significantly improves quality of life and has no significant effect on mortality.				

STUDY DETAILS: RCT		
Citation		
Tsuboi M, Ezaki K, Tobinai K, Ohashi Y, Saijo N (2009) Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: Results of a multicenter, phase III, randomized, double-blind, placebo-controlled study. Jpn J Clin Oncol 39(3):163–8.		
Affiliation/Source of funds		
Funding: Chugai Pharmaceutical Co., Ltd, Tokyo, Japan. Affiliations: Department of General Thoracic and Thyroid Surgery, Tokyo Medical University Hospital, Tokyo, Department of Internal Medicine, Fujita Health University School of Medicine, Aichi, Hematology and Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo and National Cancer Center Hospital East, Chiba, Japan.		
Study design	Level of evidence	Location/setting
RCT, double blinded	Level II	11 centres in Japan
Intervention	Comparator	
EPO 36,000IU subcut weekly for 8 weeks	Placebo subcut	

Population characteristics				
Patients of age 20 to 80 years, with lung cancer or malignant lymphoma, receiving chemotherapy with at least two cycles scheduled after the first study drug administration, Hb 8–11 g/dL, an Eastern Cooperative Oncology Group performance status (PS) ≤2, life expectancy ≥3 months as well as adequate renal and liver function. Oral iron-supplementing drugs were administered if serum iron saturation fell below 15% or MCV fell <80 μm^3.				
Length of follow-up		Outcomes measured		
Median 670 days for EPO group and 641 for placebo group.		Change in Hb from baseline, change in the Functional Assessment of Cancer Therapy Anemia total Fatigue Subscale Score (FSS) (0–52, where a higher score means less fatigue) from baseline to last evaluation, RBC transfusion requirement, nadir hemoglobin level, proportion of patients who achieved a hemoglobin level increase 2.0 g/dl from baseline, proportion of the patients with haemoglobin level ,8.0 g/dl during the study and incidence of either RBC transfusion or hemoglobin level ,8.0 g/dl.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Quality rating: Fair The method of treatment allocation was not reported. The method for dealing with missing data in QOL analysis led to an overestimation of the effect. Consequently the per protocol data has been extracted.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	63		59	
Efficacy analysis (ITT)	61		56	
Efficacy analysis (PP)				
Safety analysis				
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
FACT-Anaemia Fatigue subscale score (mean change form baseline, excludes 2 placebo subjects with missing data)	All subjects			P=0.082
	-0.5±9.4 N=61	-3.6±9.0 N=53		
	Baseline FSS ≤36			
	2.1±11.7 N=29	-1.3±9.6 N=28		P=0.225
	Baseline FSS >36			
	-2.9±5.9 N=32	-7.9±9.4 N=25		P=0.016
Transfusion incidence	7/61 (11.5%)	7/56 (12.5%)		P=0.865

Thromboembolic events	1/62	0/57		
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of lung cancer and malignant lymphoma patients with anaemia				
Applicability				
The study was performed at multiple centres in Japan. The results of the study may be applicable to the Australian setting.				
Comments				
The authors conclude that EPO treatment reduces QOL decline in patients with chemotherapy-induced anaemia.				

STUDY DETAILS: RCT		
Citation		
Auerbach M, Silberstein PT, Webb T, Averyanova S, Ciuleanu T-E, Shao J, Bridges K. (2010) Darbepoetin alfa 300 or 500 μg once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. American Journal of Haemotology 85:655–663.		
Affiliation/Source of funds		
Financial conflict-of-interest disclosures are as follows: Drs. Auerbach, Webb, and Averyanova do not have conflicts to disclose. Dr. Ciuleanu is a member of the Amgen advisory board; Drs. Ciuleanu and Silberstein have received honoraria from Amgen. Mr. Shao was an employee of Amgen with ownership of Amgen stock at the time the study was conducted. Dr. Bridges is an employee of Amgen and owns Amgen stock.		
Study design	Level of evidence	Location/setting
RCT	II	Multicentre (USA and Europe)

Intervention	Comparator
DAR 300 μg once every 3 weeks + IV iron DAR 500 μg once every 3 weeks + IV iron	DAR 300 μg once every 3 weeks DAR 500 μg once every 3 weeks
Population characteristics	
Eligible patients (≥18 years of age at screening) had active non-myeloid malignancies, anemia (screening haemoglobin ≤10 g dL^{-1}) related to cancer and chemotherapy, ≥8 additional weeks of planned chemotherapy, adequate renal and liver function, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.	
Length of follow-up	Outcomes measured
15 weeks	Mortality RBC transfusion Thromboembolic events
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Good	

RESULTS				
Population analysed	Intervention		Comparator	
Randomised	DAR 300 µg + IV iron: 60 DAR 500 µg + IV iron: 61		DAR 300 µg: 62 DAR 500 µg: 60	
Efficacy analysis (ITT)	DAR 300 µg + IV iron: 56 DAR 500 µg + IV iron: 60		DAR 300 µg: 62 DAR 500 µg: 60	
Efficacy analysis (PP)	DAR 300 µg + IV iron: 38 DAR 500 µg + IV iron: 48		DAR 300 µg: 44 DAR 500 µg: 44	
Safety analysis	DAR 300 µg + IV iron: 56 DAR 500 µg + IV iron: 60		DAR 300 µg: 62 DAR 500 µg: 60	
Outcome	IV iorn n/N (%) Mean ± SD (N)	Oral iron n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Kaplan-Meier percentage mean (95% CI) RBC transfusion incidence (N=238)	28 (20, 37)	30 (23, 39)	NR	NR
Crude percentage mean (95% CI) RBC transfusion incidence (N=238)	28 (19, 36)	29 (21, 37)	NR	NR
Embolism/thrombosis, n/N (%)	8/117 (7)	10/121 (8)		
Myocardial infarction/artery disorders, n/N (%)	2/117 (2)	2/121 (2)		
Cerebrovascular accident, n/N (%)	1/117 (1)	0/121 (0)		
Mortality, n/N (%)	8/117 (7)	13/121 (11)		
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to anaemic patients with cancer.				
Applicability				
The study is mostly applicable to the Australian context.				
Comments				

STUDY DETAILS: RCT				
Citation				
Bastit L, Vandebroek A, Altintas S, Gaede B, Pintet T, Suto TS, Mossman TW, Smith KE, Vansteenkiste JF. (2008) Randomized, Multicenter, Controlled Trial Comparing the Efficacy and Safety of Darbepoetin Alfa Administered Every 3 Weeks With or Without Intravenous Iron in Patients With Chemotherapy-Induced Anemia. Journal of Clinical Oncology 26(10): 1611–8.				
Affiliation/Source of funds				
Employment: Tamas S. Suto, Amgen; Tony W. Mossman, Amgen; Kay E. Smith, Amgen Leadership: N/A Consultant: N/A Stock: Kay E. Smith, Amgen Honoraria: Johan F. Vansteenkiste, Amgen Research Funds: Johan F. Vansteenkiste, Funds, Educational Amgen Chair in Supportive Cancer Care at the Leuven University				
Study design	Level of evidence		Location/setting	
RCT	II		Multicentre (Europe)	
Intervention		Comparator		
IV iron and 500 µg DAR every 3 weeks for 16 weeks		500 µg DAR every 3 weeks with oral iron or no iron therapy for 16 weeks		
Population characteristics				
Anaemic (Hb <11 g/dL) patients with non-myeloid malignancies				
Length of follow-up		Outcomes measured		
16 weeks		Mortality RBC transfusion Thromboembolic events Functional/performance status		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	201		197	
Efficacy analysis (ITT)	200		196	
Efficacy analysis (PP)	134		147	
Safety analysis	203		193	
Outcome	IV iron n/N (%) Mean ± SD (N)	No IV iron n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Kaplan-Meier proportion of patients receiving a RBC transfusion, % (N=396)	16	25	NR	*Favours IV iron* P=0.038

Embolism/thrombosis, arterial and venous, n/N (%)	12/203 (6)	12/193 (6)		
Myocardial infarction, ischemic and coronary artery disease, n/N (%)	3/203 (1)	1/193 (1)		
Cerebrovascular accident, n/N (%)	0/203 (0)	0/193 (0)		
Mortality, n/N (%)	21/203 (10)	15/193 (8)		
Mean (SD) FACT-F score at baseline	30.85 (11.16)	32.98 (11.24)		
Mean (95% CI) adjusted change in FACT-F score from baseline at follow-up	2.40 (0.84, 3.95)	2.17 (0.65, 3.69)	NR	P>0.05
Kaplan-Meier proportion (95% CI) of patients with a clinically meaningful increase in FACT-F score (≥3 points), %	76 (67, 84)	67 (56, 78)	NR	P>0.05
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to anaemic patients with cancer.				
Applicability				
The study is mostly applicable to the Australian context.				
Comments				

STUDY DETAILS: RCT		
Citation		
Dangsuwan P, Manchana T. (2010) Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy. Gynecologic oncology 116:522–5.		
Affiliation/Source of funds		
The authors declare that there are no conflicts of interest.		
Study design	Level of evidence	Location/setting
RCT	II	Thailand

Intervention	Comparator
The study group received 200 mg of iron sucrose (Venofer®) by intravenous drip over 30 minutes	The control group received 200 mg of oral ferrous three times a day.

Population characteristics				
Eligible patients had ovarian cancer, endometrial cancer, or synchronous ovarian and endometrial cancer. They underwent primary surgery and were receiving first-line platinum-based chemotherapy during August 2008 to July 2009. Chemotherapy regimens included single agent carboplatin and combinations of carboplatin with paclitaxel or docetaxel. All of them met criteria for RBC transfusion which was defined as hemoglobin level below 10 g/dl.				
Length of follow-up		Outcomes measured		
Consecutive cycle of chemotherapy		RBC transfusion Functional/performance status		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	22		22	
Efficacy analysis (ITT)	22		22	
Efficacy analysis (PP)	22		22	
Safety analysis	22		22	
Outcome	IV iron n/N (%) Mean ± SD (N)	No IV iron n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Incidence of RBC transfusion in consecutive cycle of chemotherapy, n/N (%)	5/22 (22.7)	14/22 (63.6)	NR	P<0.05
Median (range) volume of RBCs transfused, units	0 (0 to 2)	1 (0 to 2)	NR	P=0.01
Median (range) FACT-anaemia score at baseline	118.2 (83.5 to 153.0)	123.8 (97.0 to 165.6)	NR	P>0.05
Median (range) FACT-anaemia score after treatment	123.7 (87.0 to 151.0)	125.8 (98.1 to 165.0)	NR	P>0.05
Median (range) change in FACT-anaemia score from baseline	1.7 (−9.2 to 16.8)	0.5(−19.0 to 18.5)	NR	P>0.05
EXTERNAL VALIDITY				
Generalisability				

The study is somewhat generalisable to cancer patients with anaemia
Applicability
The study is somewhat applicable to the Aus context.
Comments

STUDY DETAILS: RCT		
Citation		
Hedenus M, Birgegard G, Nasman P, Ahlberg L, Karlsson T, Lauri B, Lundin J, Larfars G, Osterborg A. (2007) Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia 21: 627–32.		
Affiliation/Source of fund		
This work was supported by grants from Roche AB, Sweden, and the Research and Development Centre, Sundsvall Hospital, Sundsvall, Sweden. This investigator-initiated study was supported in part by research funding from Roche AB, Sweden.		
Study design	Level of evidence	Location/setting
RCT	II	Sweden
Intervention	Comparator	
subcutaneous epoetin beta 30 000 IU once weekly for 16 weeks plus IV iron (100 mg once weekly from weeks 0 to 6 followed by 100 mg every second week from weeks 8 to 14)	subcutaneous epoetin beta 30 000 IU once weekly for 16 weeks	
Population characteristics		
Eligible patients were adults with a diagnosis of clinically stable lymphoproliferative malignancy (indolent non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) or multiple myeloma (MM)) not requiring chemotherapy or blood transfusions, an Hb level of 9–11 g/dl (measured on two occasions within 1 month and an interval of at least 2 weeks), and demonstration of stainable iron in a bone marrow aspirate within 1 month before inclusion.		
Length of follow-up	Outcomes measured	
16 weeks	Mortality	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Poor		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	33	34
Efficacy analysis (ITT)	33	34

Efficacy analysis (PP)	27		30	
Safety analysis	33		34	
Outcome	IV iron n/N (%) Mean ± SD (N)	No IV iron n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mortality, n/N (%)	0/33 (0.0)	4/34 (11.8)		
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to anaemic patients with stable lymphoproliferative malignancies				
Applicability				
Mostly applicable to the Australian context.				
Comments				

STUDY DETAILS: RCT		
Citation		
Pedrazzoli P, Farris A, Del Prete S, Del Gaizo F, Ferrari D, Bianchessi C, Colucci G, Desogus A, Gamucci T, Pappalardo A, Fornarini G, Pozzi P, Fabi A, Labianca R, Di Costanzo F, Secondino S, Crucitta E, Apolloni F, Del Santo A, Siena S. (2008) Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alfa. Journal of Clinical Oncology 26(10):1615–25.		
Affiliation/Source of funds		
Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors. Employment or Leadership Position: Enrico Crucitta, Dompe´ Biotec (C); Federica Apolloni, Dompe´ Biotec (C); Antonio Del Santo, Dompe´ Biotec (C) Consultant or Advisory Role: Paolo Pedrazzoli, Dompe´ Biotec (C); Teresa Gamucci, Dompe´ Biotec (C) Stock Ownership: None Honoraria: Giuseppe Colucci, Dompe´ Biotec; Roberto Labianca, Dompe´ Biotec; Francesco Di Costanzo, Dompe´ Biotec; Salvatore Siena, Dompe´ Biotec Research Funding: None Expert Testimony: None Other Remuneration: None		
Study design	Level of evidence	Location/setting
RCT	II	Italy
Intervention	Comparator	
DA 150 g/wk for 12 weeks plus sodium ferric gluconate 125 mg/wkIV for the first 6 weeks	DA only for 12 weeks.	
Population characteristics		
For entry into the study, patients were required to have a diagnosis of breast, colorectal, lung, or gynecologic cancer and at least 12 additional weeks of planned cancer chemotherapy. Patients were eligible for the study if they were at least 18 years of age, had an Eastern Cooperative Oncology Group performance status ≤2, a life expectancy of at least 6monthsand had adequate renal and hepatic function. Patients were required to have anaemia (ie, haemoglobin (Hb) level of ≤11 g/dL) within 24 hours of random assignment, secondary to malignancy and chemotherapy treatment and not to harbor absolute or functional iron deficiency (ie, having serum ferritin level ≥100 ng/mL and transferrin saturation (TSAT) ≤20%).		
Length of follow-up	Outcomes measured	

12 weeks	Mortality RBC transfusion Thromboembolic events

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	73		76	
Efficacy analysis (ITT)	73		76	
Efficacy analysis (PP)	53		50	
Safety analysis	73		76	
Outcome	IV iron n/N (%) Mean ± SD (N)	No IV iron n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Incidence of RBC transfusion, n/N (%)	2/73 (2.7)	5/76 (6.6)		
Vascular/thromboembolic events, n/N (%)	3/73 (4.1)	2/76 (2.6)		
Mortality, n/N (%)	4/73 (5.5)	3/76 (3.9)		
EXTERNAL VALIDITY				
Generalisability				
The study is mostly generalisable to patients with chemotherapy-related anaemia without iron deficiency				
Applicability				
They study is somewhat applicable to the Aus context.				
Comments				

STUDY DETAILS: SR/MA
Citation
Desai A, Lewis E, Solomon S, McMurray JJV, and Pfeffer M. (2010) Impact of erythropoiesis-stimulating agents on morbidity and mortality in patients with heart failure: An updated, post-TREAT meta-analysis. European Journal of Heart Failure 12:936–942.
Affiliation/Source of funds

Dr. Desai reports receiving consulting fees from Intel, Relypsa, and Biogen-Idec and grant support from AtCor Medical, Inc. Dr. Lewis reports receiving consulting fees from Amgen and grant support from Amgen and the Robert Wood Johnson Foundation. Dr. Solomon reports receiving grant support from Amgen. Dr. McMurray reports receiving consulting fees from Menarini, Bristol-Myers Squibb, Roche, Novocardia, Boehringer Ingelheim, Novartis, BioMe´rieux, and Boston Scientific, lecture fees from AstraZeneca, Solvay, Takeda, Novartis, BMS Sanofi, and Vox Media, and grant support from BMS, Novartis, Amgen, AstraZeneca, Cytokinetics, Hoffmann–La Roche, Pfizer, Scios, and GlaxoSmithKline. Dr. Pfeffer reports receiving consulting fees from Abbott, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Centocor, CVRx, Genentech, Cytokinetics, Daiichi Sankyo, Genzyme, Medtronic, Novartis, Roche, Sanofi-Aventis, Servier, and VIA Pharmaceutics and grant support from Amgen, Baxter, Celladon, Novartis, and Sanofi-Aventis.				
Study design	Level of evidence		Location/setting	
SR of RCTs	I			
Intervention		Comparator		
ESAs		No ESAs		
Population characteristics				
Patients with CHF				
Length of follow-up		Outcomes measured		
NR		Morbidity and mortality		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description:				
RESULTS				
Outcome No. trials (No. patients)	ESAs n/N (%) Mean ± SD (N)	Control n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Mortality 9 trials (N=2039) [the authors excluded Silberberg et al [2001] due to concerns regarding the lack of blinding, lack of placebo control, and potential confounding by concomitant administration of IV iron to ESA-administered patients.]	224/1023 (21.9)	236/1016 (23.2)	RR 1.03 (0.89, 1.21)	*Favours control* P=0.68 *No significant heterogeneity*[a] P=0.26 (I^2=10.11)

Heart failure 9 trials (N=2039) [the authors excluded Silberberg et al [2001] due to concerns regarding the lack of blinding, lack of placebo control, and potential confounding by concomitant administration of IV iron to ESA-administered patients.]	236/1023 (23.0)	269/1016 (26.5)	RR 0.95 (0.82, 1.10)	*Favours ESAs* P=0.46 *No significant heterogeneity*[a] P=0.37 (I^2=7.62)
EXTERNAL VALIDITY				
Generalisability				
Generalisable to adults with anaemia of heart failure				
Applicability				
Applicable to the Australian context.				
Comments				
The meta-analysis included a subpopulation from the TREAT trial (Pfeffer et al [2009]). This trial randomised 4044 patients with type 2 diabetes mellitus, chronic kidney disease, and anaemia (haemoglobin ≤ 11.0 g/dL) to treatment with DAR or placebo. Desai et al (2010) incorporated the 33.4% of TREAT subjects (1347 of 4038) who were reported to have had a history of heart failure at baseline.				

STUDY DETAILS: SR/MA		
Citation		
Jin B, Luo X, Lin H, Li J, and Shi H. (2010) A meta-analysis of erythropoiesis-stimulating agents in anaemic patients with chronic heart failure. European Journal of Heart Failure 12:249–253.		
Affiliation/Source of funds		
Supported in part by the 11th Five-year National Science Project on Chronic Heart Failure in China.		
Study design	Level of evidence	Location/setting
SR	I	USA (Mancini 2003), Israel (Silverberg 2001), Italy (Palazzuoli 2007), Greece (Kourea 2008), Multicentre (Van Velahuisen 2008, Ponikowski 2007, Ghali 2008)

Intervention	Comparator
ESAs	No ESAs
Population characteristics	
Anaemic patients with CHF N=678	

Length of follow-up	Outcomes measured
NA	Mortality, Left ventricular ejection fraction, improvement in Patient Global Assessment
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Good Description:	
RESULTS	

Outcome No. trials (No. patients)	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Findings consistent with Ngo 2010				
EXTERNAL VALIDITY				
Generalisability				
Generalisable to anaemic patients with HF				
Applicability				
Mostly applicable to the Australian context. Patient Global Assessment Multicentre (Europe) and USA All cause mortality Multicentre (Europe, USA), USA, Israel, Italy, Greece				
Comments				
Findings consistent with Ngo 2010. Pooled results need to be interpreted with caution. One included study was open label.				

STUDY DETAILS: SR/MA		
Citation		
Lawler PR, Filion KB, and Eisenberg MJ. (2010) Correcting anemia in heart failure: The efficacy and safety of erythropoiesis-stimulating agents. Journal of Cardiac Failure 16:649–658.		
Affiliation/Source of funds		
Disclosures: Dr. Eisenberg is a National Researcher of the Quebec Foundation for Health Research.		
Study design	Level of evidence	Location/setting
SR of RCTs	I	Location of individual trials NR

Intervention	Comparator
ESAs	No ESAs
Population characteristics	
Anaemic patients with HF N=747	

Length of follow-up			Outcomes measured	
3–13 months follow-up			Haemoglobin concentration, BNP [brain natiuretic peptide], LVEF [left ventricular ejection fraction], hospitalisations from congestive heart failure, all-cause mortality,	
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description:				
RESULTS				
Outcome No. trials (No. patients)	ESAs n/N (%) Mean ± SD (N)	No ESAs n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
All cause mortality, n/N (%) 9 trials (N=747)	22/407 (5.4)	30/340 (8.8)	OR 0.60 (0.32, 1.11)	*Favours ESAs* P>0.05 *No significant heterogeneity* P=NR (I^2=0%)
CHF exacerbations, n/N (%) Number of trials NR (N=619)	52/342 (15.2)	60/277 (21.7)	NR	NR
Transient ischemic attack or cerebrovascular accident, n/N (%) Number of trials NR (N=596)	10/327 (3.1)	5/269 (1.9)	NR	NR
Hospitalisations from congestive heart failure	Results consistent with Ngo 2010			
NYHA symptom class				
Quality of life (Minnesota Living with Heart Failure Questionnaire and the Kansas City Cardiomyopathy Questionnaire)				
Exercise duration				
Exercise tolerance (6MWT)				
MI				

Thrombosis	
EXTERNAL VALIDITY	
Generalisability	
Generalisable to anaemic patients with HF	
Applicability	
Mostly applicable to the Australian context	
Comments	

STUDY DETAILS: SR/MA		
Citation		
Ngo K, Kotecha D, Walters JAE, Palazzuoli A, van Veldhuisen DJ, Flather M. (2010) Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD007613. DOI: 10.1002/14651858.CD007613.pub2.		
Affiliation/Source of funds		
Clinical Trials and Evaluation Unit, Royal Brompton Hospital, UK. Ongoing grant funding		
Study design	Level of evidence	Location/setting
SR of RCTs	I	UK (Cleland 2005), Belgium (Cosyns 2008), USA (Ghali 2008, Mancini 2003), Greece (Kourea 2008, Parissis 2008), Italy (Palazzuoli 2006, Palazzuoli 2007), Israel (Silverberg 2001), Multicentre (Ponikowski 2007, van Veldhuisen 2007),
Intervention	Comparator	
EPO or DAR with or without iron therapy	Placebo or no treatment	
Population characteristics		
Chronic heart failure patients with anaemia N=794		
Length of follow-up	Outcomes measured	

2 months (Cleland 2005, Cosyns 2008), 3 months (Kourea 2008a, Mancini 2003, Parissis 2008), 26 weeks (Ponikowski 2007, van Veldhuisen 2007), mean 8.2 months (Silverberg 2001), 1 year (Ghali 2008, Palazzuoli 2006, Palazzuoli 2007)	Primary Exercise tolerance as assessed by any functional capacity test, including treadmill exercise duration, the 6-minute walk test and peak VO2. Secondary 1. Measure of anaemia correction: Change in haemoglobin (Hb) level. 2. New York Heart Association (NYHA) functional classification. 3. Quality of life (QoL). 4. Haemodynamic effects: Left ventricular ejection fraction (LVEF). 5. Disease progression: CHF-related hospital admissions and B-type natriuretic peptide (BNP). 6. All-cause mortality. 7. Adverse effects of specific interest including hypertension, stroke, myocardial infarction, and other thromboembolic effects.

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Good quality

Description: Adequate search strategy used; inclusion criteria appropriate and applied in an unbiased way; quality assessment undertaken; characteristics and results of individual studies appropriately summarised; methods for pooling data appropriate; sources of heterogeneity explored

RESULTS

Outcome No. trials (No. patients)	ESA n/N (%) Mean ± SD (N)	Control n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Exercise duration (bike and treadmill), sec 4 studies (N=362); 2 good quality, 1 fair quality, 1 poor quality	NR (190)	NR (172)	MD 96.82 (5.22, 188.42)	*Favours ESA* P=0.038 *Substantial heterogeneity*[a] P=0.01 (I^2=75%)
Distance on 6-minute walk, m 4 studies (N=261); 1 good, 2 fair, 1 poor	NR (167)	NR (94)	MD 69.33 (16.99, 121.67)	*Favours ESA* P=0.0094 *Substantial heterogeneity*[a] P=0.02 (I^2=70%)
NYHA functional class improvement 8 studies (N=657); 2 good, 4 fair, 2 poor	NR (370)	NR (287)	MD -0.73 (-1.11, -0.36)	*Favours ESA* P=0.00013 *Substantial heterogeneity*[a] P<0.001 (I^2=95%)

Kansas City cardiomyopathy Questionnaire (overall summary score) 3 studies (N=247); 2 good, 1 fair	NR (150)	NR (97)	MD 4.60 (0.46, 8.75)	*Favours ESA* P=0.030 *Moderate heterogeneity*[a] P=0.16 (I^2=45%)
Kansas City cardiomyopathy Questionnaire (clinical summary score) 3 studies (N=247); 2 good, 1 fair	NR	NR	MD 7.10 (2.77, 11.43)	*Favours ESA* P=0.0013 *Substantial heterogeneity*[a] P=0.02 (I^2=76%)
Minnesota living with heart failure questionnaire (total score) 3 studies (N=462); all good quality	NR (265)	NR (197)	MD -2.02 (-5.78, 1.73)	*Favours ESA* P=0.29 *No significant heterogeneity*[a] P=0.78 (I^2=0.0%)
Patient's global assessment (reported improvement) 4 studies (N=548); 3 good quality, 1 poor quality	214/306 (69.9)	149/242 (61.6)	RR 1.16 (1.02, 1.32)	*Favours ESA* P=0.02 *Substantial heterogeneity*[a] P=0.01 (I^2=75%)
Mortality 10 studies (N=764); 3 good, 4 fair, 3 poor	25/426 (5.9)	35/338 (10.4)	RR 0.61 (0.37, 0.99)	*Favours ESA* P=0.045 *No significant heterogeneity*[a] P=0.67 (I^2=0.0%)
Stroke 8 studies (N=700); 3 good quality, 3 fair, 1 poor	7/389 (1.8)	4/311 (1.3)	RR 1.57 (0.52, 4.70)	*Favours control* P=0.42 *No significant heterogeneity*[a] P=0.86 (I^2=0.0%)
CHF-related hospitalisations 9 studies (N=734); 3 good quality, 4 fair, 2 poor	48/412 (11.7)	66/322 (20.5)	RR 0.62 (0.44, 0.87)	*Favours ESA* P=0.0051 *No significant heterogeneity*[a] P=0.72 (I^2=0.0%)

Myocardial infarction 9 studies (N=732); 3 good quality, 4 fair, 2 poor	9/410 (2.2)	12/322 (3.7)	RR 0.69 (0.31, 1.55)	*Favours ESA* P=0.37 *No significant heterogeneity*[a] P=0.94 (I^2=0.0%)
Other thromboembolic events 9 studies (N=741); 3 good quality, 4 fair quality; 2 poor quality	4/410 (1.0)	6/331 (1.8)	RR 0.65 (0.22, 1.88)	*Favours ESA* P=0.42 *No significant heterogeneity*[a] P=0.59 (I^2=0.0%)

EXTERNAL VALIDITY

Generalisability

The review is generalisable to patients with chronic heart failure

Applicability

Mostly applicable to the Australian context.

Exercise duration (bike and treadmill)
Mostly USA (N=283) as well as Italy and Greece
Distance on 6-minute walk test
Europe (165, multicentre), Greece, USA
NYHA functional class improvement
Europe (N=165; multicentre), Belgium, USA (N=270), Greece, Italy, Israel
Kansas City cardiomyopathy Questionnaire (overall summary score)
Two multicentre studies (Europe), Greece
Minnesota living with heart failure questionnaire (total score)
Multicentre (Europe), USA
Patient's global assessment (reported improvement)
Multicentre (Europe) and USA
Mortality
USA, Greece, UK, Italy, Israel, Multicentre (Europe)
Stroke
UK, USA, Greece, Italy, Multicentre (Europe)
CHF-related hospitalisations
USA, Greece, UK, Italy, Multicentre (Europe)
Myocardial infarction
UK, USA, Greece, Italy, Multicentre (Europe)
Other thromboembolic effects
UK, USA, Greece, Italy, Multicentre (Europe)

Comments

Despite the limitations of this systematic review, we have found evidence to suggest that ESAs may improve anaemia and provide clinical benefits when added to routine CHF therapy to those in mild to moderately-anaemic patients with symptomatic CHF. Specifically, ESAs appear to improve exercise tolerance, increase cardiac function and relieve symptoms when dosed to haemoglobin levels ranging from 11.5 to 15g/dL. There is also evidence for an apparent reduction in morbidity and mortality, although confirmation will require trials of greater duration and sample size. The question of whether ESAs affect the risk of adverse effects in CHF remains unanswered, although we did not identify any significant increase in these outcomes in patients treated with ESAs. Several questions deserve further investigation. The criteria for anaemia in CHF should be determined as CHF patients with subnormal haemoglobin levels are frequently undetected. As part of the criteria, an algorithm for the initial evaluation of anaemia in CHF should be developed, taking into account haemodilution, renal dysfunction and iron-deficiency assessment. There is a need to determine themechanisms by which ESAs affect cardiac function, for example the improvement in anaemia and any direct actions on cardiomyocytes. Potential for resistance to ESA therapy warrants monitoring of baseline parameters (e.g. haemoglobin levels, iron parameters, inflammatory markers and serum EPO levels) in future studies to understand the dose-response relationship. The interaction between ESAs and iron therapy should be quantified to ensure optimal dosing regimes. In addition, the interaction between ESA treatment with routine CHFmedication should be addressed, beginning with clear documentation of concurrent medication and comorbidities. Of considerable importance is clarifying the issues of benefit onmortality and adverse effects. Although the RED-HF trial should provide answers in terms of effects on mortality and morbidity, the optimal haemoglobin level for ESA therapy has yet to be addressed.

STUDY DETAILS: SR/MA		
Citation		
Tehrani F, Dhesi P, Daneshvar D, Phan A, Rafique A, Siegel RJ, and Cercek B. (2009) Erythropoiesis stimulating agents in heart failure patients with anemia: A meta-analysis. Cardiovascular Drugs and Therapy 23:511–518.		
Affiliation/Source of funds		
NR		
Study design	Level of evidence	Location/setting
SR	I	Location of individual studies NR
Intervention	Comparator	
ESAs	No ESAs	
Population characteristics		
Anaemic patients with HF N=663		
Length of follow-up	Outcomes measured	
NR	Haemoglobin levels, exercise duration, change in New York Heart Association functional class, 6-minute walk, brain natriuretic peptide level, peak oxygen consumptions	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description:		
RESULTS		

Outcome No. trials (No. patients)	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Results for exercise duration, change in New York Heart Association functional class and 6-minute walk consistent with results from Ngo 2010				
EXTERNAL VALIDITY				
Generalisability				
Generalisable to anaemic adults with HF				
Applicability				
Comments				

STUDY DETAILS: SR/MA				
Citation				
van der Meer P, Groenveld HF, Januzzi J, and van Veldhuisen DJ. (2009) Erythropoietin treatment in patients with chronic heart failure: A meta-analysis. Heart 95:1309–1314.				
Affiliation/Source of funds				
This work was supported by the Netherlands Heart Foundation (D97–017 to DJvV) and The Netherlands Organization for Scientific Research (Rubicon grant: 825–07–011 to PvdM). The funding source did not have any influence on the conduction and interpretation of the study.				
Study design	Level of evidence		Location/setting	
SR	I		Italy (Palazzouli 2006), Israel (Silverberg 2001), USA (Ghali 2008, Mancini 2003), Greece (Paussis 2008), Multicentre (Ponikowski 2007, Van Veldhuisen 2007	
Intervention		Comparator		
EPO		Placebo or standard care		
Population characteristics				
Anaemic patients with HF N=650				
Length of follow-up		Outcomes measured		
NA		Mortality, hospitalisation for HF		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description:				
RESULTS				
Outcome No. trials (No. patients)	EPO n/N (%) Mean ± SD (N)	No EPO n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Mortality, n/N (%) 7 trials (N=650); 3 good quality, 2 fair quality, 2 poor quality	20/363 (5.5)	25/287 (8.7)	RR 0.69 (0.39, 1.23)	*Favours intervention* P=0.21 *No significant heterogeneity*[a] P=0.448 (I^2=0.0%)
Hospitalisation for heart failure 7 trials (N=650); 3 good quality, 2 fair quality, 2 poor quality	37/363 (10.2)	56/287 (19.5)	RR 0.59 (0.41, 0.86)	*Favours intervention* P=0.006 No significant heterogeneity[a] P=0.389 (I^2=4.3%)

Venous thrombosis 7 trials (N=650); 3 good quality, 2 fair quality, 2 poor quality	0/363 (0.0)	3/287 (1.0)	NR	NR
DVT 7 trials (N=650); 3 good quality, 2 fair quality, 2 poor quality	0/363 (0.0)	2/287 (0.7)	NR	NR
PE 7 trials (N=650); 3 good quality, 2 fair quality, 2 poor quality	0/363 (0.0)	1/287 (0.3)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Generalisable to adults with anaemia of HF				
Applicability				
Comments				

STUDY DETAILS: RCT		
Citation		
Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Luscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, Eisenhart Rothe BE, Pocock SJ, Poole-Wilson PA, and Ponikowski P. (2009) Ferric carboxymaltose in patients with heart failure and iron deficiency. New England Journal of Medicine 361:2436–2448.		
Affiliation/Source of funds		
Sponsored by Vifor Pharma. Dr. Anker reports receiving lecture fees from Roche Pharma and Teva; Drs. Anker, Comin Colet, Filippatos, Willenheimer, Dickstein, Lüscher, and Ponikowski, fees from Vifor Pharma as members of the FAIR-HF Executive Committee; Drs. Anker, Willenheimer, and Ponikowski, lecture and consulting fees from Vifor Pharma and Amgen; and Dr. Willenheimer, lecture fees from Merck and Servier; Dr. Kirwan reports being an employee of SOCAR Research, which received fees from Vifor Pharma; Drs. Mori and von Eisenhart Rothe report being employees of Vifor Pharma and owning stock in Galenica; and Dr. Pocock reports receiving fees from Vifor Pharma as the FAIR-HF consultant statistician. Financial and other disclosures provided by the authors are available with the full text of this article at NEJM.org.		
Study design	Level of evidence	Location/setting
RCT	II	75 sites in 11 countries

Intervention	Comparator
200 mg IV iron for 24 weeks. Ferric carboxymaltose administered as an IV bolus injection of 4 mL weekly until iron until iron repletion was achieved (the correction phase) and then every 4 weeks during the maintenance phase, which started at week 8 or week 12, depending on the required iron-repletion dose.	Matching placebo
Population characteristics	
Ambulatory patients who had chronic heart failure of NYHA class II or III, a left ventricular ejection fraction of 40% or less (for patients in NYHA class II) or 45% or less (for patients in NYHA class III), a haemoglobin level at the screening visit between 95 and 135 g per liter, and iron deficiency.	
Length of follow-up	Outcomes measured
24 weeks	Mortality Thromboembolic events Functional/performance status
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Good	
RESULTS	

Population analysed	Intervention		Comparator	
Randomised	304		155	
Efficacy analysis (ITT)	304		155	
Efficacy analysis (PP)	278		135	
Safety analysis	305		154	
Outcome	IV iron n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Patients with an improvement in Self-Reported Patient Global Assessment at week 24, n/N (%)	224/304 (73.7)	82/155 (52.9)	OR 2.49 (1.66, 3.74) [calculated using Rev Man)	Favours IV iron P<0.0001
	Subgroup analyses found no significant interaction between improvement in patient Global Assessment and baseline haemoglobin concentration (≤120 or >120 g/L), baseline ferrite concentration (≤39 or >39 µg/L), baseline estimated GFR (<60 or ≥60 mL/min/1.73 m^2 of body-surface area), age (≤69.7 or >69.7 years), gender, NYHA class, baseline median LV ejection fraction (≤33% or >33%), heart failure type (non-ischemic or ischemic), presence of diabetes, median BMI (≤ 27.37 or >27.37)			

Patients with an improvement in Self-Reported Patient Global Assessment at week 12 weeks, n/N (%)	NR	NR	NR	Favours iron P<0.001
Patients with an improvement in Self-Reported Patient Global Assessment at week 4, n/N (%)	NR	NR	NR	Favours iron P<0.001
Patients with an improvement in NYHA functional class at 24 weeks, n/N (%)	NR	NR	OR 2.40 (1.55, 3.71)	Favours IV iron P<0.001
	Subgroup analyses found no significant interaction between improvement in NYHA functional class and baseline haemoglobin concentration (≤120 or >120 g/L), baseline ferrite concentration (≤39 or >39 µg/L), baseline estimated GFR (<60 or ≥60 mL/min/1.73 m^2 of body-surface area), age (≤69.7 or >69.7 years), gender, NYHA class, baseline median LV ejection fraction (≤33% or >33%), heart failure type (non-ischemic or ischemic), presence of diabetes, median BMI (≤ 27.37 or >27.37)			
Patients with an improvement in NYHA functional class at 12 weeks, n/N (%)	NR	NR	NR	Favours IV iron P<0.001
Patients with an improvement in NYHA functional class at 4 weeks, n/N (%)	NR	NR	NR	Favours IV iron P<0.001
Mean (SD) 6MWT distance at baseline, m (N=458)	274 (6)	269 (9)	NR	NR
Mean (SD) change in 6MWT distance from baseline at 4 weeks follow-up, m (N=428)	NR	NR	Mean study-treatment effect: 21 (6)	Favours IV iron P<0.001
Mean (SD) change in 6MWT distance from baseline at 12 weeks follow-up, m (N=421)	NR	NR	Mean study-treatment effect: 37 (7)	Favours IV iron P<0.001

Mean (SD) change in 6MWT distance from baseline at 24weeks follow-up, m (N=402)	NR	NR	Mean study-treatment effect: 35 (8)	Favours IV iron P<0.001
Mean (SD) EQ-5D score at baseline (N=447)	54 (1)	54 (1)	NR	NR
Mean (SD) change in EQ-5D score from baseline at 4 weeks follow-up (N=414)	NR	NR	Mean study-treatment effect: 6 (1)	Favours IV iron P<0.001
Mean (SD) change in EQ-5D score from baseline at 12 weeks follow-up (N=428)	NR	NR	Mean study-treatment effect: 6 (2)	Favours IV iron P<0.001
Mean (SD) change in EQ-5D score from baseline at 24 weeks follow-up (N=431)	NR	NR	Mean study-treatment effect: 7 (2)	Favours IV iron P<0.001
Mean (SD) Kansas City Cardiomyopathy Questionnaire score at baseline (N=448)	52 (1)	53 (1)	NR	NR
Mean (SD) change in Kansas City Cardiomyopathy Questionnaire score from baseline at 4 weeks follow-up (N=417)	NR	NR	Mean study-treatment effect: 6 (1)	Favours IV iron P<0.001
Mean (SD) change in Kansas City Cardiomyopathy Questionnaire score from baseline at 12 weeks follow-up (N=430)	NR	NR	Mean study-treatment effect: 8 (2)	P<0.001

Mean (SD) change in Kansas City Cardiomyopathy Questionnaire score from baseline at 24 weeks follow-up (N=431)	NR	NR	Mean study-treatment effect: 7 (2)	P<0.001
Mortality, n/N (%)	5/305 (1.6)	4/154 (2.6)	NR	P=0.47
Mortality due to cardiovascular causes, n/N (%)	4/305 (1.3)	4/154 (2.6)	NR	P=0.31
Hospitalisation for any cardiovascular cause, n/N (%)	16/305 (5.2)	18/154 (11.7)	NR	P=0.30
Hospitalisation for worsening heart failure, n/N (%)	7/305 (2.3)	9/154 (5.8)	NR	P=0.11
Cardiac disorder, n/N (%)	46/305 (15.1)	49/154 (31.8)	NR	P<0.01
Cardiac disorder (SAEs), n/N (%)	12/305 (3.9)	23/154 (14.9)	NR	P<0.01
Vascular disorder, n/N (%)	24/305 (7.9)	13/154 (8.4)	NR	P>0.05
Vascular disorder (SAEs), n/N (%)	3/305 (1.0)	1/154 (0.6)	NR	P>0.05
EXTERNAL VALIDITY				
Generalisability				
Generalisable to iron deficient patients with CHF.				
Applicability				
Mostly applicable to the Aus context.				
Comments				

STUDY DETAILS: RCT
Citation
Okonko DO, Grzeslo A, Witkowski T, Mandal AKJ, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, Ponikowski P. (2008) Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency. FERRIC-HF: A Randomized, Controlled, Observer-Blinded Trial. Journal of the American College of Cardiology 51:103–112.
Affiliation/Source of funds

Intravenous iron was supplied by Vifor International (St. Galen, Switzerland). An unrestricted grant was provided by Vifor International to Imperial College London. Drs. Ponikowski and Anker are consultants to Vifor International and have spoken at symposia. Dr. Poole-Wilson has attended Vifor advisory meetings.				
Study design	Level of evidence		Location/setting	
RCT (observer-blinded)	II		UK and Poland	
Intervention	Comparator			
16 weeks of IV iron (200 mg weekly until ferritin>500ng/mL, 200 mg monthly thereafter)	Standard care			
Population characteristics				
Eligibility criteria were age ≥ 21 years; symptomatic CHF (New York Heart Association [NYHA] functional class II or III); exercise limitation as evidenced by a reproducible pVO2/kg ≤18 ml/kg/min during screening; average of 2 screening Hb concentrations <12.5 g/dl (anaemic group) or 12.5 to 14.5 g/dl (non-anaemic group); ferritin <100 µg/l or between 100 g/l and 300 µg/l with a transferrin saturation (TSAT) < 20%; left ventricular ejection fraction ≤ 45% measured within the preceding 6 months using echocardiography or magnetic resonance imaging.				
Length of follow-up	Outcomes measured			
16 weeks	Mortality Thromboembolic events Performance/functional status			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	24		11	
Efficacy analysis (ITT)	24		11	
Efficacy analysis (PP)	20		10	
Safety analysis	24		11	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Baseline mean (SD) NYHA functional class	2.5 (0.5)	2.4 (0.5)	NR	NR
Baseline mean (SD) NYHA functional class (anaemic patients) [anaemic: <12.5 g/dL)	2.4 (0.5)	2.5 (0.5)	NR	NR

Baseline mean (SD) NYHA functional class (non-anaemic patients)	2.6 (0.5)	2.4 (0.5)	NR	NR
Mean (SD) change in NYHA functional class from baseline	-0.4 (0.6)	0.2 (0.4)	Treatment effect -0.6 (-0.9, -0.2)	P=0.007
Mean (SD) change in NYHA functional class from baseline (anaemic patients)	-0.3 (0.5)	0.2 (0.4)	Treatment effect -0.5 (-1.0, 0)	P=0.048
Mean (SD) change in NYHA functional class from baseline (non-anaemic patients)	-0.4 (0.7)	0.2 (0.4)	Treatment effect -0.6 (-1.3, 0.1)	P=0.08
Mean (SD) change in patient global assessment score from baseline	1.5 (1.2)	-0.2 (1.6)	Treatment effect 1.7 (0.7, 2.6)	P=0.002
Baseline mean (SD) Minnesota Living With Heart Failure Questionnaire (MLHFQ) score	41 (22)	46 (18)	NR	NR
Mean (SD) change in MLHFQ score from baseline	-10 (18)	3 (19)	Treatment effect -13 (-26, 1)	P=0.07
Baseline mean (SD) VAS fatigue score	6 (1)	6 (1)	NR	NR
Mean (SD) change in VAS fatigue score from baseline	-2 (2)	0 (2)	-2 (-3, -1)	P=0.004
Baseline mean (SD) Exercise duration, s [Excercise testing was performed on a treadmill using a modified Naughton or modified Bruce protocol depending on the physician's judgement]	476 (185)	501 (179)	NR	NR
Baseline mean (SD) Exercise duration, s (anaemic patients)	441 (188)	506 (71)	NR	NR

Baseline mean (SD) Exercise duration, s (non-anaemic patients)	510 (180)	492 (270)	NR	NR
Mean (SD) change in exercise duration from baseline, s	45 (84)	-15 (109)	Treatment effect 60 (-6, 126)	P=0.08
Mean (SD) change in exercise duration from baseline, s (anaemic patients)	63 (97)	20 (114)	Treatment effect 43 (-66, 153)	P=0.41
Mean (SD) change in exercise duration from baseline, s (non-anaemic patients)	27 (66)	-55 (98)	Treatment effect 83 (-3, 169)	P=0.06
Transient ischemic attack, n/N (%)	1/24 (4.2)	0/11 (0)	NR	NR
Mortality, n/N (%)	1/24 (4.2)	0/11 (0)	NR	NR
Mortality, n/N (%) (anaemic patients)	1/12 (8.3)	0/6 (0)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Generalisable to CHF patients with iron deficiency				
Applicability				
Mostly applicable to the AUS context.				
Comments				

STUDY DETAILS: SR/MA		
Citation		
Cody JD, Daly C, Campbell MK, Khan I, Rabindranath KS, Vale L, Wallace SA, Macleod AM, Grant A, Pennington S. (2005) Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. Cochrane Database of Systematic Reviews Issure 3. Art. No.: CD003266. DOI: 10.1002/14651858.CD003266.pub2.		
Affiliation/Source of funds		
Funded by the Chief Scientist's Office, Scottish Office Department of Health. This systematic review was initially one of six funded (in 1996) by Janssen Cilag who are manufacturers of Eprex (erythropoietin alpha) a recombinant human erythropoietin. Our contract stated that the University of Aberdeen owned the intellectual property rights and we had the right to publish the results without restriction. No industry funding was sought for the update of this review.		
Study design	Level of evidence	Location/setting

SR of RCTs and quasi-RCTs	I	The included RCTs were conducted in USA, Sweden (Clyne 1992), Japan (Kuriyama 1997), India (Ganguli 2003), and Czech republic (Teplan 2001, 2003).

Intervention	Comparator
rHu EPO	No treatment or placebo

Population characteristics

Patients with the anaemia of CKD who have not yet commenced dialysis were included. The definitions of anaemia and CKD used by each individual study were accepted. There were no age exclusions.

N=461

Length of follow-up	Outcomes measured
36 weeks (Kuryama 1997); 48 weeks (Roth 1994); 3 months (Teehan 1989); 6 months (Ganguli 2003); 1 year (Brown 1995); 3 years (Teplan 2001, Teplan 2003); 8–12 weeks (all the other RCTs)	1. Measures of progression of renal failure: time from start of rHu EPO to start of dialysis; numbers starting RRT in each group; glomerular filtration rate (GFR) at the end of the study; change in GFR; serum creatinine at the end of the study and change in creatinine in each group. Accepted methods for measurement of GFR were inulin clearance, any isotopic measure and formula based estimated GFR (e.g. MDRD and Cockcroft Gault). 2. Measures of correction of anaemia: haemoglobin/ haematocrit values; numbers of blood transfusions. 3. Quality of life measures, including changes in exercise capacity. 4. Measures of hypertension: systolic blood pressure; diastolic blood pressure; numbers with an increase or introduction of antihypertensive treatment. 5. Other adverse events: numbers discontinued due to adverse events; access problems for patients commenced on haemodialysis; seizures. 6. Mortality.

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Good

Description:

RESULTS

Outcome No. trials (No. patients)	rHu EPO n/N (%) Mean ± SD (N)	No rHu EPO n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Number of patients transfused 3 studies (N=111) between 8–48 weeks follow-up	4/61 (6.6)	13/50 (26.0)	RR 0.32 (0.12, 0.83)	*Favours rHu EPO* P=0.020 *No significant heterogeneity*[a] P=60 (I^2=0.0%)

Quality of life measures at the end of the study[b] 1 study (N=14) EXCLUDED: not a validated measure 8–12 weeks follow-up	-68 ± 22 (7)	-33 ± 21 (7)	MD -35.00 (-57.53, -12.47)	*Favours rHu EPO* *P<0.05*
Quality of life measures at the end of the study (results from studies not included in meta-analysis) 8 weeks – 6 month follow-up	Roth 1994 used a health-related quality of life (HRQL) assessment carried out at 16, 32 and 48 weeks. Scales from the Sickness Impact Profile (SIP) were used. Four scales taken from the Medical Outcomes Study Short Form and other Medical Outcome Study measures, which have demonstrated acceptable validity and reliability, were also included. During the 48 weeks of follow up the control group showed a significant decrease in physical function (P = 0.03); those receiving rHu EPO showed significant increases in energy (P = 0.045) and physical function (P = 0.015). The results from Kleinman 1989 and Roth 1994 could not be combined as different measures were used. Lim 1989 reported that all 11 participants who received rHu EPO in his trial experienced an increased sense of well-being, felt more energetic and were more able to perform their work. Ganguli 2003 reported a significant improvement in quality of life and work capacity in those receiving EPO.			
Change in exercise capacity, W[c] 1 study (N=22) 8–12 weeks follow-up	-147 ± 57 (12)	-101 ± 50 (10)	MD -46.00 (-90.73, -1.27)	*Favours rHu EPO* P<0.05
Change in exercise capacity (results from studies not included in the meta-analysis) EXCLUDED: not a validated measure 3 month follow-up	Participants in Teehan 1991 completed questionnaires before and after the study, rating their energy levels and ability to do work during the previous week. Teehan 1991 concluded that correction of anaemia was associated with significant improvements in participants' energy levels.			
Number discontinued due to adverse events[d] 4 studies (N=223) 8 weeks to 3 months	11/141 (7.8)	7/82 (8.5)	RR 0.86 (0.28, 2.59)	*Non-significantly favours rHu EPO* P=0.78 *No significant heterogeneity[a]* P=0.31 (I^2=17%)

Adverse events (results from studies not included in the meta-analysis) 8–48 weeks	Eschbach 1989 and Roth 1994 both reported "no adverse events attributable to rHu EPO therapy".			
Access problems for patient commenced on haemodialysis 8–12 weeks	Kleinman 1989 was the only trial to report on venous access (arterio- venous fistula/synthetic graft) problems. Two of seven participants in each group had either an arterio-venous fistula or bovine graft in preparation for haemodialysis and there were no clotting episodes.			
Mortality 3 studies[e] (N=168) 8–48 weeks follow-up	3/94 (3.2)	3/74 (4.1)	RR 0.60 (0.13, 2.88)	*Non-significantly favours rHu EPO* P=0.52 *No significant heterogeneity*[a] P=0.60 (I^2=0.0%)
EXTERNAL VALIDITY				
Generalisability				
Generalisable to a population of pre-dialysis patients with chronic renal failure anaemia				
Applicability				
Number of patients transfused All studies were conducted in the USA Quality of life Both Kleinman 1989 and Roth 1994 were conducted in the USA Exercise capacity Clyne 1992 was conducted in Sweden, Teehan in the USA Discontinuation due to adverse events All studies were conducted in the USA (including the studies not in MA) Mortality One study was conducted in Japan, the other two in the USA (the study that found no deaths was also conducted in the USA)				
Comments				
The benefits of rHu EPO treatment in predialysis participants are that it corrects anaemia and avoids the requirement for blood transfusions. In the long term the critical question as to whether treatment with rHu EPO either speeds or delays the onset of RRT remains unanswered.				

STUDY DETAILS: SR/MA
Citation
Gandra SR, Finkelstein FO, Bennett AV, Lewis EF, Brazg T, Martin ML. (2010) Impact of erythropoiesis-stimulating agents on energy and physical function in nondialysis CKD patients with anemia: a systematic review. Am J Kidney Dis 55:519–534.

Affiliation/Source of funds				
This research was supported by Amgen Inc, which markets ESAs. Dr Gandra is an employee of Amgen Inc. Dr Finkelstein has received research funding and advisory board honoraria from Amgen. Antonia V. Bennett, Tracy Brazg, and Mona L. Martin have received research funding from Amgen. Dr Lewis has received consulting fees and research grant support from Amgen.				
Study design	Level of evidence		Location/setting	
SR	I		Location of included studies NR	
Intervention		Comparator		
ESAs (EPO or DAR)		No ESAs		
Population characteristics				
Non-dialysis CKD patients N=2870				
Length of follow-up		Outcomes measured		
8–48 weeks		Energy and physical function		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description:				
RESULTS				
Outcome No. trials (No. patients)	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Energy and fatigue	Consistent with results from Cody 2005 and Tonelli 2008			
EXTERNAL VALIDITY				
Generalisability				
Applicability				
Comments				

STUDY DETAILS: SR/MA
Citation
Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C, Mayne TJ. (2010) Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis 55:535–548.
Affiliation/Source of funds

This study was conceived by employees of Amgen Inc, which markets ESAs; Dr Gitlin is an employee of Amgen Inc. Dr Mayne formerly was an employee of Amgen Inc. Drs Johansen and Finkelstein have received research support from Amgen Inc. Dr Revicki and his employer United Biosource Corp, as well as Dr Evans and his employer MapiValues, have received consulting fees and research support from Amgen Inc.				
Study design	Level of evidence		Location/setting	
SR of RCTs and cohort studies	I		Location of included studies NR	
Intervention		Comparator		
-		-		
Population characteristics				
Anaemic adults with on-dialysis ESRD N=777				
Length of follow-up		Outcomes measured		
-		-		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description:				
RESULTS				
Outcome No. trials (No. patients)	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Agrees with results from Cody 2005 and Tonelli 2008				
EXTERNAL VALIDITY				
Generalisability				
-				
Applicability				
-				
Comments				
-				

STUDY DETAILS: SR/MA
Citation
Tonelli M, Klarenbach S, Wiebe N, Shrive F, Hemmelgarn B, Manns B. Erythropoiesis-Stimulating Agents for Anemia of Chronic Kidney Disease: Systematic Review and Economic Evaluation [Technology report number 106]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.
Affiliation/Source of funds

Dr. Tonelli, Dr. Hemmelgarn, Dr. Manns, and Dr. Klarenbach are members of the Alberta Kidney Disease Network (AKDN). This research group has received research support from Amgen Canada -none of the research being conducted by the Alberta Kidney Disease Network is directly related to anemia. Amgen Canada does not have any input into the type of research that is conducted by the AKDN, nor does it review any research that is produced by the AKDN before publication.

Dr. David Mendelssohn has received speaking honoraria and served on advisory boards for Ortho Biotech, Amgen, Roche, and several other companies.

Ortho Biotech provides unrestricted financial support in the form of a fellowship (salary award) to some of Dr. Garg's physician trainees who pursue research training.

Study design	Level of evidence	Location/setting
SR	I	Czech republic (Teplan 2003), Israel (Silverberg 2001), Japan (Kuriyama 1997), USA (Nissenson 1995, Teehan 1991, Roth 1994, Abraham 1991, Bennett 1991,), Eastern Europe (Klinkmann 1993), Germany (Bahlmann 1991), Canada (CESG 1990)

Intervention	Comparator
epoetin (alpha or beta), darbepoetin or "management without ESA" (no ESA) Hb targets ranged from 95 g/L to 140 g/L. Two trials targeted Hb <100 g/L and four trials > 120 g/L.	The following comparisons were assessed • ESA vs no ESA • high vs intermediate or low Hb target strategies • darbepoetin vs epoetin • dosage • schedule • route or administration

Population characteristics

Adult patients with anaemia of chronic kidney disease (CKD) who need or do not need dialysis.

N=1553 (ESA vs no ESA)

Ten trials compared ESA to no ESA. Four trials included patients with non-dialysis-dependent CKD, one was in peritoneal dialysis and the remaining five in haemodialysis patients. The mean age range of study participants was 45–69 years and the proportion of males ranged from 32% to 60%. Mean baseline Hb ranged from 70 g/L to 102 g/L and was not reported in two trials. The median time on dialysis ranged from 3.3 years to 4.4 years. Baseline renal function was not consistently reported and few trials reported comorbidities among study participants.

Length of follow-up	Outcomes measured
Median duration of follow-up: 26 weeks (range 5–156 weeks) 5 weeks (Silverberg 2001) 12 weeks (Abraham 1991, Bennett 1991, Nissenson 1995) ≤26 weeks (Bahlmann 1991) 36 weeks (Kuriyama 1997) 48 weeks (Roth) 1 year (Klinkmann 1993) 3 years (Teplan 2003)	• mortality (all-cause, cardiovascular) • cardiovascular events [MI, stroke, congestive heart failure (CHF), revascularization] • hospitalization (all-cause, cardiovascular) • vascular access loss or dialysis dependence • renal function (GFR, CrCl, SCr) • QoL [fatigue domain from the Kidney Disease Questionnaire (KDQ)26 and all eight domains from the SF-36]27 • red cell transfusions • blood pressure • left ventricular mass index • AEs.

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Good

Description:

RESULTS

Outcome No. trials (No. patients)	ESA n/N (%) Mean ± SD (N)	No ESA n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
All-cause mortality 7 studies (N=1048); 1 good quality, 1 poor quality, 5 fair quality 12 weeks to 1 year follow-up	19/575 (3.3)	26/473 (5.5)	RR 0.71 (0.40, 1.24)	*Favours ESA* P=0.23 *No significant heterogeneity*[a] P=0.80 (I^2=0)
All-cause mortality (non-dialysis dependent CKD patients) 2 studies (N=156); both fair quality	1/85 (1.2)	3/71 (4.2)	RR 0.35 (0.05, 2.30)	*Favours ESA* P=0.27 *No significant heterogeneity*[a] P=0.93 (I^2=0)
All-cause mortality (peritoneal dialysis patients) 1 studies (N=152); good quality	2/78 (2.6)	1/74 (1.4)	RR 1.90 (0.18, 20.49)	*Favours no ESA* P=0.60

All-cause mortality (haemodialysis patients) 4 studies (N=740); 1 poor quality, 3 fair quality	16/412 (3.9)	22/328 (6.7)	RR 0.71 (0.39, 1.31)	*Favours ESA* P=0.28 *No significant heterogeneity*[a] P=0.60 (I^2=0)
Cardiovascular mortality 3 studies (N=564); 1 poor quality, 2 fair quality ≤26 weeks to 1 year follow-up	1/286 (0.3)	12/278 (4.3); NB: 9 of the mortality cases occurred in Klinkmann 1993 (N=181).	RR 0.15 (0.03, 0.69)	*Favours ESA* P=0.01 *No significant heterogeneity*[a] P=0.84 (I^2=0)
Cardiovascular mortality (non-dialysis dependent CKD patients) 1 study (N=73); fair quality	0/42 (0.0)	2/31 (6.5)	RR 0.15 (0.01, 2.99)	*Favours ESA* P=0.21
Cardiovascular mortality (haemodialysis patients) 2 studies (N=491); 1 poor quality, 1 fair quality	1/244 (0.4)	10/247 (4.0)	RR 0.16 (0.03, 0.88)	*Favours ESA* P=0.03 *No significant heterogeneity*[a] P=0.55 (I^2=0)
Myocardial infarction 2 studies (N=445); 1 poor quality, 1 fair quality 48 weeks to 1 year follow-up	2/224 (0.9)	4/221 (1.8)	RR 0.56 (0.12, 2.62)	*Favours ESA* P=0.46 *No significant heterogeneity*[a] P=0.68 (I^2=0)
Stroke 1 study (N=129); fair quality ≤26 weeks follow-up	0/63 (0.0)	1/66 (1.5)	RR 0.35 (0.01, 8.41)	*Favours ESA* P=0.52

Heart failure 2 studies (N=445); 1 poor quality, 1 fair quality 48 weeks to 1 year follow-up	5/224 (2.2)	13/221 (5.9)	RR 0.41 (0.15, 1.07)	*Favours ESA* P=0.07 *No significant heterogeneity*[a] P=0.86 (I^2=0)
Vascular access thrombosis 1 study (N=118); fair quality 26 weeks follow-up	NR	NR	RR 5.64 (0.75, 42.16)	*Favours no ESA* P>0.05
Change in health-related quality of life (KDQ – fatigue) 1 study (N=98); fair quality 26 weeks follow-up	-	-	WMD 1.10 (0.76, 1.44)	*Favours ESA* P<0.001
Red cell transfusions (non-dialysis dependent CKD) 1 study (N=83); fair quality ≤26–48 weeks follow-up	4/43 (9.3)	9/40 (22.5)	RR 0.41 (0.14, 1.24)	*Favours ESA* P=0.11
Red cell transfusions (haemodialysis) 2 studies (N=217); both fair quality	7/131 (5.3)	51/86 (59.3)	RR 0.09 (0.03, 0.32)	*Favours ESA* P=0.0001 *Substantial heterogeneity*[a] P=0.13 (I^2=56.2)
Withdrawal from medication or study due to adverse event 3 studies (N=343); 1 good quality, 1 fair quality, 1 poor quality	13/190 (6.8)	5/153 (3.3)	RR 2.10 (0.77, 5.71)	*Favours no ESA* P=0.15 *No significant heterogeneity*[a] P=0.68 (I^2=0)

Serious adverse event 2 studies (N=269); 1 good quality, 1 fair quality	5/164 (3.0)	16/105 (15.2)	RR 0.29 (0.12, 0.73)	*Favours ESA* P=0.009 *No significant heterogeneity*[a] P=0.58. (I^2=0)
Any adverse event 3 studies (N=366); 1 good quality, 2 fair quality	132/211 (62.6)	94/155 (60.6)	RR 1.02 (0.81, 1.30)	*Favours no ESA* P=0.84 *Substantial heterogeneity*[a] P=0.13. (I^2=50.5)
EXTERNAL VALIDITY				
Generalisability				
Generalisable to adult patients with anaemia of chronic kidney disease (CKD) who need or do not need dialysis.				
Applicability				
All-cause mortality The studies were conducted in Canada, Japan, USA, Germany, and Eastern Europe Cardiovascular mortality The studies were conducted in Japan in non-dialysis dependent CKD patients, and Germany and Eastern Europe for heamodialysis patients. Myocardial infarction The studies were conducted in Eastern Europe and USA Stroke The study was conducted in Germany Heart failure The studies were conducted in Eastern Europe and USA Health related quality of life The study was conducted in Canada Red cell transfusions The study was conducted in USA in non-dialysis dependent CKD patients; Germany and Canada in haemodialysis patients Withdrawal due to adverse events Canada, Eastern Europe, and USA Serious adverse events Both USA Any adverse event All USA				

Comments
Conclusions • Health outcomes are improved, but some uncertainty remains. ESA resulted in lower observed cardiovascular mortality, but allcause mortality was not affected. The impact on health-related quality of life was modest, and most trials did not provide a complete report of these measures. • Intermediate and low targets are optimal. Low (90 to 105 g/L) Hb target strategies represent the least costly and second most effective option. Intermediate Hb target (110g/L) strategies produce the largest number of quality-adjusted life years (QALYs) at an additional cost per patient lifetime (C$21,000 to C$27,000 per patient lifetime compared with the low Hb target in non-dialysis dependent and dialysis-dependent adult CKD). • Route of administration and Hb target will affect health care budgets. For dialysis dependent patients, the estimated cost of treating anaemia to an intermediate Hb target is C$9,394 per patient per year on dialysis. If SC epoetin is used instead of IV (or if darbepoetin is used via either route), costs could be reduced to C$6,577 per patient per year. Altering the Hb target to a low strategy would result in cost savings of C$35 million to C$49 million per year compared with the intermediate target. Outcomes not data extracted There was no significant difference in initiation of dialysis, There was a significantly smaller loss of GFR with ESA compared with no ESA (WMD [95% CI] 2.01 mL/min [0.67, 3.34]; N=151). SBP and DBP WMDs were statistically significant and mainly showed BP reductions among control patients and increases in ESA patients. The WMDs were 6.1 mmg Hg (95% CI: 1.8; 10.4); I^2=0% for SBP and 5.5 mm Hg (95% CI: 3.0, 8.1); I^2=0% for DBP. One trial reported change in mean arterial pressure, although there were no significant differences between groups.

STUDY DETAILS: RCT		
Citation		
Cianciaruso B; Ravani P, Barrett BJ, Levin A. (2008) Italian randomized trial of hemoglobin maintenance to prevent or delay left ventricular hypertrophy in chronic kidney disease. J Nephrol. 21: 861–870.		
Affiliation/Source of funds		
Study data were provided by Janssen-Cilag SpA, Italy, but independentrly analysed and used for manuscript writing.		
Study design	Level of evidence	Location/setting
RCT	II	Italy (in tertiary-care hospitals in Italy)

Intervention	Comparator
Epoetin-α as needed to maintain Hgb levels in the target range of 12 to 14 g/dL ± 0.5 g/dL and not to exceed 14 g/dL When indicated by protocol for either group, epoetin-α therapy was commenced at 2,000 IU once weekly subcutaneously, with protocoled adjustments to maintain the prespecified targets. Oral or IV iron supplementation was administered as necessary to maintain transferring saturation at 20% or greater and serum ferrite level at 60 ng/mL or greater.	No epoetin-α unless Hgb ≤ 9.0 g/dL, at which point epoetin-α could be administered to maintain their Hgb levels between 9.0 and 10.5 g/dL
Population characteristics	
Pre-dialysis CKD patients Patients were required to be between 18 and 75 years of age, to have a calculated creatinine clearance (using the Cockcroft-Gault formula) of 15 to 79 ml/min and (i) either a demonstrated progressive decline in hemoglobin (Hgb) level of 1.0 g/dL or greater within the previous 12 months to a current Hgb level between 11.0 and 13.5 g/dL for men and 10.0 and 13.5 g/dL for women; or (ii) a current Hgb level between 11.5 and 12.5 g/dL for men and 11.0 and 12.0 g/dL for women. Those with known reversible causes of anemia or decline in Hgb levels (including iron insufficiency, serum ferritin level <60 ng/mL and/or transferrin saturation <20%) were excluded.	
Length of follow-up	Outcomes measured
1 year The median time between baseline and follow-up echocardiogram was 385 days (IQR 340–421)	LV mass index change was the primary outcome variable and residual renal function a secondary efficacy variable. In the absence of a 24-month measurement, any measurement at least 10 months after the initial one, was considered acceptable for inclusion in analysis. Due to the premature study termination no patient received an echocardiogram examination after 1 year. Between-group comparisons of change over time in renal function, functional cardiac status and quality of life also were planned to be examined. Safety evaluations were based on the incidence and severity of adverse events, as well as measurements of kidney function and blood pressure.
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Good Description: Randomisation was reported and method appropriate; adequate method for allocation concealment (opaque envelopes); open label, but outcome assessments were either blinded (echocardiograms) or were not likely to be influenced by blinding of assessment (adverse events); loss to follow-up was adequately reported; baseline characteristics similar between treatment arms.	
RESULTS	

Population analysed	Intervention	Comparator
Randomised	46	49

Efficacy analysis (ITT)	37 (1 violation entry criteria; 1 brain hemorrhage; 2 worsening renal function; 5 participation discontinuation)		41 (1 violation entry criteria; 1 worsening renal function; 1 lost to observation; 5 participation discontinuation)	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	EPO-α n/N (%) Mean ± SD (N)	No EPO-α n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Decline in NYHA status at 12 months, n/N (%)	2/37 (5.4)	1/41 (2.4)	NR	*P=0.609*
Decline in CCS status at 12 months, n/N (%)	0/37 (0.0)	2/41 (4.9)	NR	P=0.495
Rupture of a cerebral aneurysm	1/37 (2.7)	0/41 (0.0)	NR	NR
Progression to end-stage renal disease requiring dialysis	4/37 (10.8)	4/41 (9.8)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients with pre-dialysis CKD				
Applicability				
The study was conducted in Italian hospitals and is therefore somewhat applicable to the Australian context.				
Comments				

STUDY DETAILS: RCT		
Citation		
Macdougall IC, Temple RM, Kwan TC. (2007) Is early treatment of anaemia with epoetin-α beneficial to pre-dialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomized, comparative group trial. Nephrol Dial Transplant 22: 784–793.		
Affiliation/Source of funds		
Funded by Ortho Biotech (a division of Janssen-Cilag)		
Study design	Level of evidence	Location/setting
RCT	II	UK (24 sites)
Intervention	Comparator	
Subcutaneous epoetin-a (SC-EPO; 1000U twice weekly) at an early stage of anaemia to maintain Hb at 11.0 ± 1.0 g/dl.	Hb allowed to fall to ≤9.0 g/dL before starting SC-EPO (2000 U three times weekly); and subsequently maintaining Hb at 11.0 ± 1.0 g/dl.	
Population characteristics		
Pre-dialysis chronic kidney disease patients Patients aged 18–85 years were required to have a diagnosis of progressive renal failure and were thought likely by the investigator to require dialysis within 1–5 years of study enrolment. Each patient had to have a serum creatinine level of 150–500 mmol/l and an Hb concentration of 11.00.5 g/dl, with no evidence of iron deficiency (i.e. serum ferritin 60 mg/l, transferrin saturation 20%, and hypochromic red cells <10%). From baseline values of 150–500 mmol/l for creatinine and 11.00.5 g/dl for Hb, both creatinine and Hb concentrations had to be considered to be deteriorating (Hb lower and creatinine higher than the preceding reading), as determined by a series of three readings over at least 3 months before enrolment. Excluded were patients who had previously received renal replacement therapy (including renal transplant), those with unstable or poorly controlled angina or severe congestive cardiac failure (New York Heart Association Grade III or IV), gross cardiomyopathy/LVH (as evidenced by screening echocardiogram), surgically placed arteriovenous fistula, poorly controlled hypertension (>160/90 mmHg), severe chronic respiratory disease, severe symptomatic peripheral vascular disease ('severe' as determined by the investigator), or those in whom LVM could not be deduced from an echocardiogram. Nor were they allowed to have haemoglobinopathies, marrow disorders or other conditions known to cause anaemia, inflammatory or infectious diseases which might impair the response to erythropoietin, prior treatment with erythropoietin or blood transfusion, or to have taken androgens or erythropoiesis-suppressing medications within 1 month of enrolment or blood transfusion for other reasons within 3 months of enrolment. Women who were pregnant, lactating or without adequate contraception were also excluded.		

Length of follow-up	Outcomes measured
Patients continued the study until 3 years or the start of renal replacement therapy or death.	LVM was calculated from an echocardiogram (Box 1). The primary efficacy variable was the greatest (worst) LVM. The greatest (worst) LVM and the change from baseline to greatest LVM, and the times to worst echo and to final echo were determined for each patient. Secondary efficacy variables included progression of renal failure (measured by serial blood creatinine measurements, creatinine clearance and yearly isotopic GFR measurement using 51chromium-labelled EDTA), exercise tolerance and final epoetin-a doses. The number of patients who withdrew because of starting dialysis or death was recorded, and the time to dialysis or death from randomization was summarized using Kaplan–Meier plots and compared between the groups. In addition, the time to dialysis or death from the start of treatment was evaluated and compared. Exercise tolerance before treatment and at 1-year intervals were assessed from the distance walked in 6 min (performed twice, second recording used for analysis). Mean last recorded scores and mean worst (shortest) scores were compared between treatment groups.

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Fair Description: Appropriate method of randomisation; allocation concealment NR; open label; outcome assessment not blinded (some outcomes including exercise tolerance are susceptible to observer bias); similar baseline characteristics between study arms; loss to follow-up adequately accounted for in the analysis.

RESULTS				
Population analysed	Intervention		Comparator	
Randomised	65		132	
Efficacy analysis (ITT)	64 (one subject randomised in error)		132	
Completed 3 years	20 (44 withdrew; 1 randomised in error)		20 (112 withdrew)	
Safety analysis	64		132	
Outcome	Epoetin-alpha n/N (%) Mean ± SD (N)	No epoetin-alpha n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Progression to treatment	NA	55/132 (41.7)	NA	NA
Mean time to trigger initiation of epoetin therapy, months	NA	13.2 ± 7.9 (132)	NA	NA
Withdrawal due to adverse event	2/65 (3.1)	8/132 (6.1)		

Withdrew due to dialysis commencement	29/65 (44.6)	61/132 (46.2)		
Withdrew due to renal transplant	0/65 (0.0)	9/132 (6.8)		
No. dialysis/death	31/64 (48.4)	68/132 (51.5)	NR	*Favours epoetin-alpha* P=0.686
Mortality	1/64 (1.6)	5/132 (3.8)[a]		
Patients on dialysis	30/64 (46.9)	63/132 (47.7)		
Mean length of time to dialysis or death, months	26.21 ± 1.49 (64)	24.71 ± 1.05 (132)	NR	NR
Median length of time to dialysis or death, months	36.26	27.34	NR	*Favours epoetin-alpha* P=0.351 (log rand test for group A vs group B comparison)
Mean distance walked in 6 min (at the last recorded exercise test), m	419.3 ± 124.4 (64)	420.5 ± 129.0 (132)	NR	*Favours control* P=0.954
Worst result for 6 min walk test, m	395.8 ± 110.5	408.4 ± 127.8	NR	*Favours control* P=0.526
Adverse events	62/65 (95.4)	126/132 (95.5)		
Serious drug-related adverse events	0/65 (0.0)	2/132 (1.5) [haematemesis, pure red cell aplasia]		
Peripheral oedema	10/65 (15.4)	10/132 (7.6)		
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to pre-dialysis chronic kidney disease patients				
Applicability				
Study is mostly applicable to Australian context				
Comments				

STUDY DETAILS: RCT		
Citation		
Pfeffer MA, Burdmann EA, Chen C-Y, Cooper ME, Zeeuw D, Eckardt K-U, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJV, Parfrey P, Parving H-H, Remuzzi G, Singh AK, Solomon SD, Toto R. (2009) A trial of dardepoetin alfa in Type 2 diabetes and chronic kidney disease. New Eng J Med. 361(21):2019–2032.		
Affiliation/Source of funds		
Supported by Amgen, which provided statistical support through a contract with the board of regents for the University of Wisconsin System for data analysis for the TREAT Data and Safety Monitoring Committee as well as for the study. Dr. Pfeffer reports receiving consulting fees from Abbott, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Centocor, CVRx, Genentech, Cytokinetics, Daiichi Sankyo, Genzyme, Medtronic, Novartis, Roche, Sanofi-Aventis, Servier, and VIA Pharmaceutics and grant support from Amgen, Baxter, Celladon, Novartis, and Sanofi-Aventis, and being named coinventor on a patent for the use of inhibitors of the renin–angiotensin system in selected survivors of myocardial infarction; Dr. Burdmann, receiving consulting fees from Amgen and Sigma Pharma and grant support from Amgen and Roche; Drs. Chen and Kewalramani, being employees of and owning stock in Amgen; Dr. Cooper, receiving consulting fees from Amgen; Dr. de Zeeuw, receiving consulting fees from Amgen and Novartis and lecture fees from Amgen; Dr. Eckardt, receiving consulting fees from Amgen, Ortho Biotech, Roche, Affymax, Stada, and Sandoz–Hexal and lecture fees from Amgen, Ortho Biotech, and Roche; Dr. Ivanovich, receiving consulting fees from Amgen, Baxter, Biogen, and Reata; Dr. Levey, receiving grant support from Amgen; Dr. Lewis, receiving consulting fees from Amgen and grant support from Amgen and the Robert Wood Johnson Foundation; Dr. McGill, receiving consulting fees from Amgen and Boehringer Ingelheim, lecture fees from Novartis, and grant support from Novartis and Boehringer Ingelheim; Dr. McMurray, receiving consulting fees from Menarini, Bristol-Myers Squibb, Roche, Novocardia, Boehringer Ingelheim, Novartis, BioMérieux, and Boston Scientific, lecture fees from AstraZeneca, Solvay, Takeda, Novartis, BMS Sanofi, and Vox Media, and grant support from BMS, Novartis, Amgen, AstraZeneca, Cytokinetics, Hoffmann–La Roche, Pfizer, Scios, and GlaxoSmithKline; Dr. Parfrey, receiving consulting and lecture fees from Amgen and lecture fees from Ortho Biotech; Dr. Parving, receiving consulting fees from Amgen and Novartis and lecture fees from Novartis; Dr. Singh, receiving consulting fees from Johnson & Johnson and Watson, lecture fees from Johnson & Johnson, Amgen, and Watson, and grant support from Johnson & Johnson, Amgen, Roche, AMAG Pharmaceuticals, and Watson; Dr. Solomon, receiving grant support from Amgen; and Dr. Toto, receiving consulting and lecture fees from Amgen and grant support from Novartis, Reata, and Abbott. No other potential conflict of interest relevant to this article was reported.		
Study design	Level of evidence	Location/setting
RCT	II	Trial was conducted at 623 sites in 24 countries: including Australia
Intervention	Comparator	
Darbepoitin alfa with dose adjusted by a point-of-care device to maintain the hemoglobin level at approximately 13.0 g/dL. Measurements of hemoglobin levels and vital signs were performed every 2 weeks during the study-drug-titration period and monthly thereafter.	Placebo. Patients received darbepoetin as a rescue agent if the haemoglobin level fell below 9.0 g/dL, with a return to placebo once the haemoglobin level was 9.0 g/dL or higher.	

Population characteristics	
Anaemic patients with type 2 diabetes and chronic kidney disease Patients with type 2 diabetes, chronic kidney disease (an estimated glomerular filtration rate [GFR] of 20 to 60 ml per minute per 1.73 m2 of bodysurface area, calculated with the use of the fourvariable Modification of Diet in Renal Disease formula), anemia (hemoglobin level, ≤11.0 g per deciliter), and a transferrin saturation of 15% or more were eligible for enrollment. Patients with any of the following factors were excluded: uncontrolled hypertension; previous kidney transplantation or scheduled receipt of a kidney transplant from a living related donor; current use of intravenous antibiotics, chemotherapy, or radiation therapy; cancer (except basal-cell or squamouscell carcinoma of the skin); diagnosed human immunodeficiency virus infection; active bleeding; a hematologic disease; or pregnancy. Patients who had had a cardiovascular event or grand mal seizure, had undergone major surgery, or had received an ESA in the 12 weeks before randomization were also ineligible.	
Length of follow-up	Outcomes measured
4 years (for all outcomes except the patient-reported outcomes, where the length of follow-up is not clear)	The primary end points were the time to the composite outcome of death from any cause or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and the time to the composite outcome of death or end-stage renal disease. Important secondary end points included time to death, death from cardiovascular causes, and the components of the primary end points, as well as the rate of decline in the estimated GFR and changes in patient-reported outcomes at week 25 measured with the use of the Functional Assessment of Cancer Therapy–Fatigue (FACT-Fatigue) instrument (on which scores range from 0 to 52, with higher scores indicating less fatigue) and the 36-Item Short-Form General Health Survey questionnaire (calculated with norm-based scoring so that 50 is the average score, with higher scores indicating a better quality of life) Safety outcomes monitored
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Good Description: Method of randomisation appropriate; allocation concealment NR; study was double blinded and outcome assessment was blinded to treatment allocation; baseline characteristics were similar between treatment arms; loss of follow-up was appropriately accounted for.	

RESULTS

Population analysed	Intervention	Comparator
Randomised	2016	2031
Efficacy analysis (ITT)	2012 (4 patients from sites that did not adhere to Good Clinical Practice guidelines were excluded)	2026 (4 patients from sites that did not adhere to Good Clinical Practice guidelines were excluded)
Efficacy analysis (PP)	NR	NR
Safety analysis	NR	NR

Outcome	Darbepoetin alfa n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
RBC transfusion incidence	297/2012 (14.8)	496/2026 (24.5)	HR 0.56 (0.49, 0.65)	*Favours darbepoetin alfa* P<0.001
Incidence of death or nonfatal cardiovascular event	632/2012 (31.4)	602/2026 (29.7)	HR 1.05 (0.94, 1.17)	*Favours placebo* P=0.41
Death from any cause	412/2012 (20.5)	395/2026 (19.5)	HR 1.05 (0.92, 1.21)	*Favours placebo* P=0.48
Myocardial infarction[a]	124/2012 (6.2)	129/2026 (6.4)	HR 0.96 (0.75, 1.22)	*Favours darbepoetin alfa* P=0.73
Stroke[a]	101/2012 (5.0)	53/2026 (2.6)	HR 1.92 (1.38, 2.68)	*Favours placebo* P<0.001
Heart failure	205/2012 (10.2)	229/2026 (11.3)	HR 0.89 (0.74, 1.08)	*Favours darbepoetin alfa* P=0.24
Myocardial ischemia	41/2012 (2.0)	49/2026 (2.4)	HR 0.84 (0.55, 1.27)	*Favours darbepoetin alfa* P=0.40
Renal composite end point (ESRD or death)	652/2012 (32.4)	618/2026 (30.5)	HR 1.06 (0.95, 1.19)	*Favours placebo* P=0.29
ESRD	338/2012 (16.8)	330/2026 (16.3)	HR 1.02 (0.87, 1.18)	*Favours placebo* P=0.83
Death from cardiovascular causes	259/2012 (12.9)	250/2026 (12.3)	HR 1.05 (0.88, 1.25)	*Favours placebo* P=0.61
Cardiac revascularisation	84/2012 (4.2)	117/2026 (5.8)	HR 0.71 (0.54, 0.94)	*Favours darbepoetin alfa* P=0.02
Mean baseline FACT-Fatigue score	30.2 ± NR (1762)	30.4 ± NR (1769)	NR	NR
Mean change in FACT-Fatigue score from baseline at Week 25	4.2 ± 10.5 (1762)	2.8 ± 10.3 (1769)	NR	*Favours darbepoetin alfa* P<0.001

Patients with an increase of three or more points in FACT-Fatigue score (considered to be clinically meaningful)	963/1762 (54.7)	875/1769 (49.5)	NR	*Favours darbepoetin alfa* P=0.002
Mean change in SF-36 (energy) [length of follow-up not clear]	2.6 ± 9.9 (1138)	2.1 ± 9.7 (1157)	NR	*Favours darbepoetin alfa* P=0.20
Mean change in SF-36 (physical functioning) [length of follow-up not clear]	1.3 ± 9.2 (1138)	1.1 ± 8.8 (1157)	NR	*Favours darbepoetin alfa* P=0.51
Antibody-mediated pure red-cell aplasia	0/2012 (0.0)	0/2026 (0.0)	NA	NA
Venous thromboembolic events	41/2012 (2.0)	23/2026 (1.1)	NR	*Favours placebo* P=0.02
Arterial thromboembolic events (some of which were adjudicated as cardiovascular events)	178/2012 (8.9)	144/2026 (7.1)	NR	*Favours placebo* P=0.04
Cancer-related adverse events	139/2012 (6.9)	130/2026 (6.4)	NR	*Favours placebo* P=0.53
Deaths attributable to cancer	39/2012 (1.9)	25/2026 (1.2)	NR	*Favours placebo* P=0.08 (by the log-rank test)
Deaths among patients with a history of a malignant condition at baseline	60/188 (31.9)	37/160 (23.1)	NR	*Favours placebo* P=0.13 (by the log-rank test)
Deaths attributable to cancer among patients with a history of malignant condition at baseline	14/188 (7.4)	1/160 (0.6)	NR	*Favours placebo* P=0.0002 (by the log-rank test)
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients with diabetes, chronic kidney disease, and moderate anaemia				

Applicability
The study is applicable to the Australian context.
Comments
It is our view that, in many patients with diabetes, chronic kidney disease, and moderate anaemia who are not undergoing dialysis, the increased risk of stroke and possibly death among patients with a history of a malignant condition will outweigh any potential benefit of an ESA.

STUDY DETAILS: RCT		
Citation		
Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A (2006) A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *Am J Nephrol* 26:445–454.		
Affiliation/Source of funds		
This study was sponsored by Watson Laboratories Inc. This trial was registered with the United States National Institutes of Health through the National Library of Medicine at http://www.clinicaltrials.gov/		
Study design	Level of evidence	Location/setting
RCT	II	Multicentre (26 sites) USA

Intervention	Comparator
IV Iron sucrose, 250mg over 1 hour, once per week	Oral Ferrous sulphate, 325mg, tid (three times daily)
Population characteristics	
Anaemic, iron-deficient adults with ND-CKD not receiving ESA treatment. (pre-dialysis) Anaemia: Hb < 12.0g/dL Iron deficiency: serum ferritin <100 ng/mL and/or TSAT (transferring saturation) <20%.	
Length of follow-up	Outcomes measured
4 weeks or more <u>Treatment duration</u> IV = 4 weeks = 22 days Oral = 6 weeks = 42 days	Functional performance (KDQoL)
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Fair Allocation generation: Adequate, Allocation concealment: Adequate	
RESULTS	

Population analysed	Intervention	Comparator

Randomised	44		45	
Efficacy analysis (ITT)	36		39	
Efficacy analysis (PP)	29		31	
Safety analysis	36		39	
Outcome	IV Mean ± SD (N)	Oral Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
KDQoL - Mean change from baseline (CFB) % on day 43 or termination				
SF-12 physical health composite	4.8 ± 8.6 * (36)	0.7 ± 8.6 (39)	NR	*No significant difference* P = 0.080
SF-12 mental health composite	3.3 ± 9.8 (36)	-0.8 ±15.1 (39)	NR	*No significant difference* P = 0.114
Burden of KD	6.4 ±19.6 (36)	-3.6 ± 25.9 (39)	NR	*No significant difference* P = 0.056
Symptoms of KD	3.0 ± 11.6 (36)	-2.7 ±17.5 (39)	NR	*Favours IV* P = 0.025
Effects of KD	2.7 ±14.5 (36)	-2.3 ± 13.13 (39)	NR	*Favours IV* P = 0.048
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to ND-CKD patients, not receiving ESA treatment.				
Applicability				
Assuming the trials were conducted in the USA, the study is applicable to the Australian healthcare context with a few caveats.				
Comments				
Specific differential effects favouring IV were seen for 'Symptoms of KD' and 'Effect of KD' because of the improvement in the scores of IV and the worsening of scores of Oral iron. Authors concluded that the improvement in QoL under IV may be independent of Hgb correction but it may expose patients to the greater risk of adverse events (not covered in the study).				

STUDY DETAILS: RCT		
Citation		
Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, and Pereira BJG. (2009) Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clinical Journal of the American Society of Nephrology* 4:386–393.		
Affiliation/Source of funds		
AMAG Pharmaceuticals, Inc. funded this study, and its employees identified study sites, monitored the study to ensure adherence to Good Clinical Practice, and performed data analyses according to the predefined statistical analysis plan. An abstract of some of these data was submitted to the October 2007 American Society of Nephrology Meeting. We gratefully acknowledge the contribution of members of the Clinical Studies Steering Committee (Drs. W. Kline Bolton, Anatole Besarab, Ajay Singh, and Bruce Spinowitz), who provided guidance throughout the study and critical review of the manuscript.		
Study design	Level of evidence	Location/setting
RCT	II	USA, Multicentre

Intervention	Comparator
IV +rHuEPO Ferumoxytol, 510mg * 2 injections over 17sec during sequential dialysis treatments (within 5± 3 days). Each dose was injected any time after 60min (± 15 min) into HD session. ESA dose was required to remain constant during the study.	Oral + rHuEPO Elemental iron, 200mg, daily (21 days) Elemental iron as Ferrous-Sequels (50mg of ferrous fumarate per tablet) ESA dose was required to remain constant during the study.

Population characteristics	
Patients on HD with iron deficiency anaemia (On-Dialysis). On HD for at least 90 days and stable ESA therapy. Anaemia: Hb ≤ 11.5g/dL. Serum ferretin ≤ 600ng/ml, TSAT ≤30%	
Length of follow-up	Outcomes measured
35 days (5 weeks)	Mortality
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Fair	
RESULTS	

Population analysed	Intervention	Comparator
Randomised	114	116
Efficacy analysis (ITT)	114	116
Efficacy analysis (PP)	102	99
Safety analysis	110	114

Outcome	IV n/N (%) Mean ± SD (N)	Oral n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mortality (N = 214, Safety)	1/110 (0.9)	3/114 (2.6)	NR RR 0.35 (0.04, 3.27) [A]	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients receiving HD and rHuEPO treatment.				
Applicability				
The study is applicable to the Australian healthcare context with few caveats.				
Comments				
Short-term follow up (5 weeks). Deaths in both the IV and oral group were not considered to be related to treatment.				

STUDY DETAILS: SR/MA		
Citation		
Rozen-Zvi B, Gafter-Gvili A, Paul M, Leibovici L, Shpilberg O, Gafter U. (2008) Intravenous versus Oral Supplementation for the Treatment of Anemia in CKD: Systematic Review and Meta-analysis. American Journal of Kidney Disease. 52: 897–906		
Affiliation/Source of funds		
Support: None. *Financial Disclosure:* None.		
Study design	Level of evidence	Location/setting
SR of RCTs	I	Multinational (USA, UK, China, Italy, India)

Intervention	Comparator
IV (with or without ESA)	Oral (with or without ESA)
Population characteristics	
Patients with CKD (stages III-V) on dialysis or not on dialysis. No Anaemia measure.	
Length of follow-up	Outcomes measured
Limited to 2–3 months. Max 6 months	Mortality Transfusion frequency (need for transfusion or anaemia intervention) Functional Performance

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: The SR compared IV vs Oral iron treatment for patients with CKD on dialysis and not on dialysis. The literature search was based on KDOQI guidelines on HD and PD-CKD, then 'iron', 'IV' 'Oral'. The SR did not search for anaemia.				
RESULTS				
Outcome No. trials (No. patients)	IV n/N (%) Mean ± SD (N)	Oral n/N (%) Mean ± SD (N)	Risk Ratio (95% CI)	Significance P-value Heterogeneity [a] P value (I^2)
All-cause Mortality[b] 5 trials (N =540)	0/260	3/280 (1.1)	0.28 (0.02, 5.22)	No difference between treatment groups
Need for blood transfusion (Transfusion frequency)[c] 2 trials (N =263)	2/120 (1.7)	3/143 (2.1)	1.36 (9.21, 8.73)	No difference between treatment groups
Functional performance – KDQoL 1 trial (N = 89)	NR	NR	NR	"An improvement in patients treated with IV iron" [d]
Functional performance – SF-36 1 trial (N = 188)	NR	NR	NR	NS
EXTERNAL VALIDITY				
Generalisability				
The review is generalisable to target population with some caveats (such as the measure of anaemia)				
Applicability				
The review is applicable to the Australian healthcare context with a few caveats.				
Comments				
See notes below regarding risk estimates.				

STUDY DETAILS: RCT
Citation
Singh H, Reed J, Noble S, Cangiano J, Van Wyck D. (2006) Effect of Intravenous Iron Sucrose in Peritoneal Dialysis Patients who Receive Erythropoiesis-Stimulating Agents for Anemia: A Randomized, Controlled Trial. Clinical Journal of the American Society of Nephrology.1(3): 475–482
Affiliation/Source of funds
This study was supported by American Regent, Inc.

Study design	Level of evidence	Location/setting
RCT	II	Various. 21 enrolment sites (27 study sites)

Intervention	Comparator
ESA + IV iron sucrose (1g of IV iron sucrose divided into 3 doses over 28 days. 300 mg over 1.5 h on days 1 and 15, 400 mg over 2.5 h on day 29). Patients received ESA at the same dose as before randomization, unchanged throughout the study period.	ESA only (No supplemental iron) Patients received ESA at the same dose as before randomization, unchanged throughout the study period.

Population characteristics
Anemic patients with peritoneal dialysis-dependent CKD (PD-CKD) Anemia: (Hb ≥ 9.5 g/dL and ≤ 12.5 g/dL). Serum ferretin ≤ 500ng/ml, TSAT ≤25% NB: a lower Hb was permitted for enrolment in the Mexican study sites (Hb ≥ 8.5 g/dL and ≤ 12.5 g/dL

Length of follow-up	Outcomes measured
12 weeks	Anemia intervention

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Poor (See quality assessment form) Description:

RESULTS

Population analysed	Intervention		Comparator	
Randomised	80		46	
Efficacy analysis (ITT)	80 NR		46 NR	
Efficacy analysis (modified ITT)	66		30	
Efficacy analysis (PP)	62		26	
Safety analysis	75		46	
Outcome	Iron Therapy n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Anemia intervention [incl. Increase in ESA dose, nonprotocol IV iron, RBC transfusion], non-completion of study (N = 121, Safety)	1/75 (1.3)	5/46 (10.9)	NR 0.12 (0.10, 1.02)[a]	

Time to anemia intervention (median days)	59	34		0.0137 (Wald X^2)

EXTERNAL VALIDITY

Generalisability

Generalisable to an adult population with PD-CKD anemia.

Applicability

No details provided on location of study sites (with the exception of Mexico and USA). Probably applicable to the Australian setting.

Comments

The authors conclude that IV iron administration increases HB without an increase in ESA dose, hence decreasing the need for anemia intervention. Previous adjuvant trials have been limited by Hb-targeting bias. Adjuvant efficacy to ESA requires maintaining constant ESA doses before and after adjuvant therapy.

The authors also highlight that the efficacy of oral iron administration adjuvant ESA therapy in PD remains unclear.

STUDY DETAILS: RCT

Citation

Stoves J, Inglis H, Newstead CG (2001). A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. Nephrol Dial Transplant 16:967–974

Affiliation/Source of funds

We thank Janssen Cilag and Syner-Med for their sponsorship of the study. JS is supported by the Yorkshire Kidney Research Fund.

Study design	Level of evidence	Location/setting
RCT	II	UK

Intervention	Comparator
IV +rHuEPO Iron sucrose, 300mg over 2hrs, monthly Initial dose of rHuEPO commenced at 2000U twice weekly. rHuEPO treatment discontinued if Hb > 14g/dL and re-intdouced with values < 12g/dL	Oral + rHuEPO Ferrous sulphate, 200mg, tds (three times a day) Initial dose of rHuEPO commenced at 2000U twice weekly. rHuEPO treatment discontinued if Hb > 14g/dL and re-intdouced with values < 12g/dL

Population characteristics

Anaemic patients with progressive renal insufficiency (PRI), serum creatinine > 250µmol/L

Not requiring dialysis. (Pre-Dialysis)

Anaemia: Hb < 11g/dL

Length of follow-up	Outcomes measured
6 months	Mortality

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Poor Allocation generation: Adequate Allocation concealment: Not specified				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	22		23	
Efficacy analysis (ITT)	22		23	
Efficacy analysis (PP)	15		17	
Safety analysis	22		22	
Outcome	IV n/N (%) Mean ± SD (N)	Oral n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Death (N = 45, ITT)	1/22 (4.5)	0/23	NR 6.13 (0.26, 144.72) 3.13 (0.13, 72.99)[a]	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients with Chronic Kidney Disease on rHuEPO treatment (not on dialysis)				
Applicability				
The study is applicable to the Australian healthcare context with few caveats.				
Comments				
The death in the intravenous iron group was presumed to have resulted from cardiovascular disease.				

STUDY DETAILS: RCT		
Citation		
Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S (2005) A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 68:2846–2856		
Affiliation/Source of funds		
This study was supported by American Regent Inc.		
Study design	Level of evidence	Location/setting
RCT	II	Multicentre (35 sites)

Intervention	Comparator
IV (+ ESA or no ESA) Iron sucrose, 1000mg over 14 days as: a) 500mg infusions in 250ml 0.9% NaCl over 3.5–4 hrs on days 0 and 14 b) 200mg undiluted injection over 2–5min over 5 days from day 0 to day 14	Oral (+ ESA or no ESA) Ferrous sulphate, 325, tds
Population characteristics	
Anaemic, iron-deficient Non-dialysis-CKD patients (stages III- V). Stable ESA or no ESA (Epoetin or darbeopoetin). Permitted oral iron treatment prior to enrolment given an 8-week interval without ESA dose change. (Pre Dialysis) Anaemia: Hb ≤ 11.0g/dL Iron deficiency: transferring saturation ≤ 25%; ferritin ≤ 300 ng/mL Exclusion: - Parenteral iron within 6 months prior to enrolment - Blood transfusion within 2 months prior to enrolment	
Length of follow-up	Outcomes measured
56 days	Transfusion frequency (Anaemia intervention: either a RBC transfusion increase in EPO or iron administration not included in protocol) Functional performance (SF-36)
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Poor Allocation generation: Not specified Allocation concealment: Not specified	

RESULTS		
Population analysed	Intervention	Comparator
Randomised	95	93
Efficacy analysis (ITT) Modified	79	82
Efficacy analysis (PP)	70	72
Safety analysis	91	91

Outcome	IV n/N (%) Mean ± SD (N)	Oral n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Anaemia intervention [defined as either a red blood cell transfusion, an increase in ESA dose, or iron administration not included in the study protocol], non completion of study N = 182, Safety	8/91 (8.8)	8/91 (8.8)	NR RR 1.00 (0.39, 2.55) [a]	NR
QoL (SF-36)	We found no statistically significant differences between the treatment groups for the mean change from baseline to day 56 in the health concept categories of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.			NS (p.2851)
Mean (SD) SF-36 change from baseline to day 56[d], m (N = 182)	NR	NR	NR	NS
SF-36 Physical Functioning (N =182)	NR	NR	NR	NS
SF-36 Role-physical (N =182)	NR	NR	NR	NS
SF-36 Bodily pain (N =182)	NR	NR	NR	NS
SF-36 Role-physical (N =182)	NR	NR	NR	NS
SF-36 Role-physical (N =182)	NR	NR	NR	NS
EXTERNAL VALIDITY				
Generalisability				
The results for transfusion frequency may be generalisable for ND-CKD patients, receiving or not receiving ESA treatment				
Applicability				
Assuming the trails were conducted in the USA, the study is applicable to the Australian healthcare context with a few caveats.				

Comments
Measure of anaemia intervention (need for blood transfusion) not a definitive measure of transfusion frequency Authors conclude that "Increased QoL is an important outcome of anemia correction. No measurable improvement in QoL was evidenced in either group, presumably because the increase in Hb was small."

STUDY DETAILS: RCT		
Citation		
Agnihotri P, Telfer M, Butt Z, Jella A, Cella D, Kozma CM, Ahuja M, Riaz S, and Akamah J. (2007) Chronic anemia and fatigue in elderly patients: Results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa. Journal of the American Geriatrics Society 55:1557–1565.		
Affiliation/Source of funds		
Ortho Biotech Clinical Affairs, LLC provided the funding and study drug. Parag Agnihotri has served as a consultant and has received grant support from Ortho Biotech and Ortho McNeil and has no stock or patents. Zeeshan Butt has served as a consultant and has received grant support from Ortho Biotech and has no stock or patents. David Cella has served as a consultant and has received grant support from Ortho Biotech and Amgen and has no stock or patents.		
Study design	Level of evidence	Location/setting
Randomised cross-over trial	II	USA

Intervention	Comparator
Once-weekly injection of subcutaneous EPO alpha for 16 weeks Patients were crossed over for the remainder of the trial (Phase II). If, at Week 8, serum ferritin was less than 20 ng/mL or transferrin saturation was less than 15%, than 325 mg twice a day of ferrous sulphate with vitamin C was prescribed for the remainder of the phase. No IV iron supplementation was given during this study.	Matched placebo If, at Week 8, serum ferritin was less than 20 ng/mL or transferring saturation was less than 15%, than 325 mg twice a day of ferrous sulphate with vitamin C was prescribed for the remainder of the phase. No IV iron supplementation was given during this study.
Population characteristics	
Ambulatory, community-dwelling adults aged 65 and older with Hb of 11.5 g/dL or less for more than 3 months.	
Length of follow-up	Outcomes measured
32 weeks (16 weeks for each phase)	Mortality Thromboembolic events Functional/performance status
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Fair	

RESULTS				
Population analysed	Intervention		Comparator	
Randomised	33		29	
Efficacy analysis (ITT)	Phase I: 32 Phase II: 24		Phase I: 26 Phase II: 30	
Efficacy analysis (PP)	Phase I: 32 Phase II: 24		Phase I: 26 Phase II: 30	
Safety analysis	Phase I: 32 Phase II: 24		Phase I: 26 Phase II: 30	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mean (SE) FACIT [Functional Assessment of Chronic Illness Therapy] – fatigue subscale (0 low to 52 high) at follow-up	Phase I 41.9 (1.0) Phase II 43.4 (2.3)	Phase I 36.4 (1.1) Phase II 33.8 (2.0)	NR	Phase I P<0.001 Phase II P=0.01
Mean (SE) FACIT – anaemia subscale (0 low to 80 high) at follow-up	Phase I 62.3 (1.2) Phase II 64.3 (2.8)	Phase I 56.3 (1.4) Phase II 53.6 (2.4)	NR	Phase I P=0.002 Phase II P=0.02
Mean (SE) FACIT – anaemia total (0 low to 188 high) at follow-up	Phase I 146.8 (2.6) Phase II 152.2 (5.3)	Phase I 137.9 (2.9) Phase II 132 (4.6)	NR	Phase I P=0.03 Phase II P=0.02
FACT [Functional Assessment of Cancer Therapy] – general (0 low to 108 high) at follow-up	Phase I 85.1 (1.5) Phase II 87.9 (2.9)	Phase I 81.6 (1.6) Phase II 78.4 (2.4)	NR	Phase I P=0.13 Phase II P=0.04
LASA [Linear Analog Scale Assessment) (0 cm low to 10 cm high) at follow-up	Phase I 7.0 (0.2) Phase II 7.3 (0.4)	Phase I 6.0 (0.3) Phase II 5.9 (0.4)	NR	Phase I P=0.02 Phase II P=0.04

TUG [Timed Up and Go] test (<20 sec normal), sec	Phase I 27.9 (2.8) Phase II 23.8 (1.7)	Phase I 27.9 (3.2) Phase II 24.5 (1.5)	NR	Phase I P=0.99 Phase II P=0.80
DVT, n/N (%)	Phase I 0/32 (0.0) Phase II 0/24 (0.0)	Phase I 1/26 (3.8) Phase II 0/30 (0.0)	NR	NR
Pulmonary embolism, n/N (%)	Phase I 0/32 (0.0) Phase II 1/24 (4.2)	Phase I 0/26 (0.0) Phase II 0/30 (0.0)	NR	NR
Stroke, n/N (%)	Phase I 0/32 (0.0) Phase II 0/24 (0.0) [Was determined to be due to underlying pre-existing atrial fibrillation (last study Hb 11.0 g/dL]	Phase I 1/26 (3.8) Phase II 0/30 (0)	NR	NR
Mortality, n/N (%)	Phase I 1/32 (3.1) [not considered to be treatment related] Phase II 0/24 (0.0)	Phase I 1/26 (3.8) [not considered to be treatment related] Phase II 0/30 (0.0)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The results of the study are somewhat generalisable to elderly patients with anaemia.				
Applicability				
The results are somewhat applicable to the AUS context.				
Comments				

STUDY DETAILS: RCT
Citation
Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, and Bowers PJ. (2004) Epoetin Alfa Maintains Ribavirin Dose in HCV-Infected Patients: A Prospective, Double-Blind, Randomized Controlled Study. Gastroenterology 126:1302–1311.

Affiliation/Source of funds				
Supported by a research grant from Ortho Biotech Products, L.P. Dr. Schiff received research support from Abbot, Amgen, Bayer, Bristol Myers Squibb, Gilead, GlaxSmithKline, Idenix, Idun, Ortho Biotech, Ortho Clinical Diagnostics, Prometheus, Roche Diagnostics, Roche Molecular, Roche Pharmaceutical, Schering Plough, SciClone Pharmaceuticals, and Wako Chemicals USA Companies.				
Study design	Level of evidence		Location/setting	
RCT	II		USA	
Intervention	Comparator			
EPO SC q.w.	Placebo			
Population characteristics				
HCV-infected patients on combination therapy (either IFN-α + ribavirin or PEG-IFN-α + ribavirin) who developed anemia (Hb ≤ 12 g/dL)				
Length of follow-up	Outcomes measured			
8-week double-blind phase followed by an 8-week open-label phase (where both arms receive EPO).	QoL, thromboembolic events, mortality			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	93		92	
Efficacy analysis (ITT)	-		-	
Efficacy analysis (PP)	83		83	
Safety analysis	83		83	
Outcome	EPO n/N (%) Mean ± SD (N)	Standard care n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mean (SD) change in LASA [linear analog scale assessment) score from baseline at 8 week follow-up	12.7 (NR)	4.8 (NR)	NR	P<0.001
Mean (SD) change in SF-36v2 (physical functioning) score from baseline at 8 week follow-up	9.7 (NR)	4.3 (NR)	NR	P<0.05

Mean (SD) change in SF-36v2 (role physical) score from baseline at 8 week follow-up	10 (NR)	0.7 (NR)	NR	P<0.05
Mean (SD) change in SF-36v2 (bodily pain) score from baseline at 8 week follow-up	8.4 (NR)	4.2 (NR)	NR	P<0.05
Mean (SD) change in SF-36v2 (general health) score from baseline at 8 week follow-up	2.7 (NR)	1.1 (NR)	NR	P>0.05
Mean (SD) change in SF-36v2 (vitality) score from baseline at 8 week follow-up	15.2 (NR)	4.1 (NR)	NR	P<0.05
Mean (SD) change in SF-36v2 (social functioning) score from baseline at 8 week follow-up	12 (NR)	2.6 (NR)	NR	P<0.05
Mean (SD) change in SF-36v2 (role emotional) score from baseline at 8 week follow-up	6.2 (NR)	-3.3 (NR)	NR	P<0.05
Mean (SD) change in SF-36v2 (mental health) score from baseline at 8 week follow-up	5.6 (NR)	0.1 (NR)	NR	P<0.05
Coronary artery disorder, n/N (%)	0/93 (0.0)	1/92 (1.1)	NR	NR
Cerebrovascular disorder/cerebral thrombosis, n/N (%)	1/93 (1.1)	0/92 (0.0)	NR	NR
Mortality, n/N (%)	1/93 (1.1)	0/92 (0.0)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to HCV-infection patients with anaemia following treatment with RBV/IFN.				
Applicability				
The study is mostly applicable to the Australian context.				
Comments				

STUDY DETAILS: RCT		
Citation		
Dieterich DT, Wasserman R, Brau N, Hassanein TI, Bini EJ, Bowers PJ, and Sulkowski MS. (2003) Once-Weekly Epoetin Alfa Improves Anemia and Facilitates Maintenance of Ribavirin Dosing in Hepatitis C Virus-Infected Patients Receiving Ribavirin Plus Interferon Alfa. American Journal of Gastroenterology 98:2491–2499.		
Affiliation/Source of funds		
This research was supported by a grant from Ortho Biotech Products; D.T.D. has received financial support for research and honoraria from and has served as a consultant to Ortho Biotech Products; R.W. has received financial support for research and honoraria from and has served as a consultant to Ortho Biotech Products; N.B. has received financial support for research and honoraria from Ortho Biotech Products; T.I.H. has received financial support for research and honoraria from and has served as a consultant to Ortho Biotech Products; E.J.B. has received financial support for research and honoraria from and has served as a consultant to Ortho Biotech Products; P.J.B. is an employee of Ortho Biotech Products; M.S.S. has received grant and/or research support from Schering-Plough, Roche Laboratories, and Ortho Biotech Products; M.S.S. is also a consultant for Schering-Plough, a member of the Speakers Bureaus for Schering-Plough and Ortho Biotech Products, and has received honoraria from Schering-Plough, Roche Laboratories, and Ortho Biotech Products.		
Study design	Level of evidence	Location/setting
RCT	II	USA
Intervention	Comparator	
EPO SC q.w.	Standard care	
Population characteristics		
HCV-infected patients who had Hb levels of 12 g/dl or less during the first 24 wk of combination RBV/IFN therapy		
Length of follow-up	Outcomes measured	
16 weeks	QoL	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Poor		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	36	28
Efficacy analysis (ITT)	-	-
Efficacy analysis (PP)	21	14
Safety analysis	21	14

Outcome	EPO n/N (%) Mean ± SD (N)	Standard care n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mean (SD) improvement in SF-12 (physical component) from baseline at 16 week follow-up	4.9 (9.1)	2.0 (10.8)	NR	NR
Mean (SD) improvement in SF-12 (mental component) from baseline at 16 week follow-up	2.7 (10.1)	0.1 (7.7)	NR	NR
Mean (SD) improvement in LASA (energy) from baseline at 16 week follow-up, mm	21.8 (22.6)	9.4 (19.9)	NR	NR
Mean (SD) improvement in LASA (activity) from baseline at 16 week follow-up, mm	16.0 (22.4)	5.3 (22.9)	NR	NR
Mean (SD) improvement in LASA (overall) from baseline at 16 week follow-up, mm	17.3 (23.1)	5.4 (21.1)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to HCV-infection patients with anaemia following treatment with RBV/IFN.				
Applicability				
The study is mostly applicable to the Australian context.				
Comments				

STUDY DETAILS: SR/MA
Citation
Marti-Carvajal AJ and Sola I. (2007) Treatment for anemia in people with AIDS. Cochrane Database of Systematic Reviews.

Affiliation/Source of funds				
No known conflicts of interest. Sources of support Universidad de Carabobo, Centro Cochrane Iberoamericano, Cochrane Collaboration Steering Group				
Study design	Level of evidence		Location/setting	
SR of RCTs	I		USA (Fischel 1990, Sulkowski 2005), Argentina (Rendo 2001)	
Intervention	Comparator			
Treatments for anaemia – rHuEPO, androgen replacement, vitamin B_{12} therapy, folic acid therapy, and darbepoetin alfa. Studies focusing on iron supplementation were excluded.	Any other intervention or placebo			
Population characteristics				
People with HIV or AIDS who also have anaemia (hb <12 g/dL in men and <11 g/dL in women). N (fischl and sulkowski) = 129 Fischl 1990 – Patients with AIDs treated with zidovudine Sulkowski 2005 was in HIV/hepatitis C virus-coinfected patients treated with interferon/ribaririn.				
Length of follow-up	Outcomes measured			
30 days (Rendo 2001) 12 weeks (Fischl 1990) 16 weeks (Sulkowski 2005)	Mortality Transfusion incidence and volume QoL			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description:				
RESULTS				
Outcome No. trials (No. patients)	EPO n/N (%) Mean ± SD (N)	Control n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Mortality, n/N 1 trial (N=63) [Fischl 1990]	0/29 (0)	2/34 (5.9)		

Incidence of allogeneic blood transfusion (patients with endogeneous EPO ≤500 IU/L), n/N (%) 1 trial (N=63) [Fischl 1990]	5/NR (NR)	17/NR (NR)	NR	P<0.05
Incidence of allogeneic blood transfusion, n/N (%) 1 trial (N=63) [Fischl 1990]	11/29 (37.9)	21/34 (61.8)	NR	P>0.05
Mean (SD) volume of RBC or whole blood transfused (patients with endogenous EPO ≤500 IU/L) , units 1 trial (N=63) [Fischl 1990]	0.84 (NR)	2.74 (NR)	NR	P<0.05
Mean (SD) volume of RBC or whole blood transfused, units 1 trial (N=63) [Fischl 1990]	1.48 (NR)	2.58 (NR)	NR	P>0.05
Change in SF-12 (physical component) score from baseline at follow-up 1 trial (N=66) [Sulkowski 2005]	6.0 (1.8)	2.2 (1.2)	NR	NR
Change in SF-12 (mental component) score from baseline at follow-up 1 trial (N=66) [Sulkowski 2005]	2.3 (2.0)	0.1 (1.5)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Difficult to generalise to all anaemic patients with AIDS.				
Applicability				
Somewhat applicable to the AUS context.				
Comments				
The results from Grossman 2003 are not discussed in this data extraction form as the study compared two different treatment frequencies of EPO. The results from Rendo 2001 are excluded because it was in a paediatric population.				

STUDY DETAILS: RCT				
Citation				
Fischl M, Galpin JE, Levine JD, Groopman JE, Henry DH, Kennedy P, Miles S, Robbins W, Starrett B, Zalusky R, Abels RI, Tsai HC, Rudnick SA (1990). Recombinant human erythropoietin for patients with AIDS treated with zidovudine. The New England Journal of Medicine 322:1488–93.				
Affiliation/Source of funds				
Supported in part by a grant from Ortho Pharmaceutical Corp				
Study design	Level of evidence		Location/setting	
RCT	II		USA	
Intervention	Comparator			
IV EPO thrice weekly (target haematocrit 0.38 to 0.40)	Placebo			
Population characteristics				
Adults with a clinical diagnosis of AIDS treated with zidovudine. Baseline haematocrit of ≤ 0.30 and either transfusion dependent or a ≥ 15% decline in haematocrit since zidovudine initiation. N=63				
Length of follow-up	Outcomes measured			
12 weeks	Mortality, RBC transfusion			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	29		34	
Efficacy analysis (ITT)	29		34	
Efficacy analysis (PP)	29		34	
Safety analysis	29		34	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mortality, n/N (%) 1 trial (N=63)	0/29 (0%)	2/34 (5.9%)	RR 0.23 (0.01, 4.67)	No significant difference P=0.34
Incidence of allogeneic blood transfusion, n/N (%) 1 trial (N=63)	11/29 (37.9)	21/34 (61.8)	NR	No significant difference P>0.05

Incidence of allogeneic blood transfusion (patients with endogenous EPO ≤500 IU/L), n/N (%) 1 trial (N=63)	5/NR (NR)	17/NR (NR)	NR	Favours EPO P<0.05
Mean (SD) volume of RBC or whole blood transfused, units 1 trial (N=63)	1.48 (NR)	2.58 (NR)	NR	No significant difference P>0.05
Mean (SD) volume of RBC or whole blood transfused (patients with endogenous EPO ≤500 IU/L), units 1 trial (N=63)	0.84 (NR)	2.74 (NR)	NR	Favours EPO P<0.05
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to patients with HIV				
Applicability				
Not applicable to current practice				
Comments				

STUDY DETAILS: RCT		
Citation		
Sulkowski MS, Dieterich DT, Bini EJ, Brau N, Alvarez D, DeJesus E et al. (2005). Epoetin alfa once weekly improves anemia in HIV/Hepatitis C virus-coinfected patients treated with interferon/ribavirin: a randomized controlled trial 39:504–6.		
Affiliation/Source of funds		
Study design	Level of evidence	Location/setting
RCT	II	USA
Intervention	Comparator	
EPO	Standard care	
Population characteristics		
Adults with a clinical diagnosis of AIDS with Hb <12 g/dL or a >2 g/dL decrease in Hb after pegylated interferon alfa plus ribavirin. N=63		

Length of follow-up	Outcomes measured
12 weeks	Mortality, RBC transfusion
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Fair	
RESULTS	

Population analysed	Intervention		Comparator	
Randomised	34		32	
Efficacy analysis (ITT)	34		32	
Efficacy analysis (PP)	34		32	
Safety analysis	34		32	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mean (SD) change in SF-12 (physical component; 0 low to 100 high) score from baseline at follow-up 1 trial (N=66)	6.0 (1.8)	2.2 (1.2)	NR	NR
Change in SF-12 (mental component; 0 low to 100 high) score from baseline at follow-up 1 trial (N=66)	2.3 (2.0)	0.1 (1.5)	NR	NR

EXTERNAL VALIDITY
Generalisability
Somewhat generalisable to patients with HIV
Applicability
Somewhat applicable to the Australian population.
Comments

STUDY DETAILS: RCT
Citation

Kulnigg S, Stoinov S, Simanenkov V, Dudar L, Karnafel W, Garcia LC, Sambuelli AM, D'Haens G, Gasche C. (2008) A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT®) randomized controlled trial. American Journal of Gastroenterology 103:1182–92.				
Affiliation/Source of funds				
This study was supported by an unrestricted scientific grant from Vifor (International), Inc., Switzerland. Performance of the trial and analysis and interpretation of the data were done by a Clinical Research Organization (PAREXEL International) on behalf of the sponsor.				
Study design	Level of evidence		Location/setting	
RCT	II		Multicentre (Europe, Mexico, and Argentina)	
Intervention	Comparator			
IV iron (maximum 1,000 mg per infusion) at 1-week intervals until the patient's calculated total iron deficit was reached.	Oral iron (100 mg b.i.d.) for 12 weeks			
Population characteristics				
Patients with either Crohn's disease or ulcerative colitis and iron deficiency anaemia (defined by Hb ≤ 10 g/dL and transferrin saturation <20% or serum ferritin <100 µg/L)				
Length of follow-up	Outcomes measured			
12 weeks	Mortality Functional/performance status			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Fair				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	137		63	
Efficacy analysis (ITT)	136		60	
Efficacy analysis (PP)	111		49	
Safety analysis	137		63	
Outcome	IV iron n/N (%) Mean ± SD (N)	Oral iron n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Median (range) SF-36 score at baseline	93.5 (54 to 134)	91.2 (50 to 136)	NR	NR
Median (range) SF-36 score at follow-up	110.3 (48 to 143)	108.3 (45 to 137)	NR	NR
Median change in SF-36 score from baseline at follow-up	14.1	8.6	NR	NR
Mortality, n/N (%)	1/137 (0.7)	0/63 (0.0)		
EXTERNAL VALIDITY				

Generalisability
The study is mostly generalisable to IBS patients with iron deficiency anaemia.
Applicability
The study is somewhat applicable to the Australian context.
Comments

STUDY DETAILS: RCT				
Citation				
Schroder O, Mickisch O, Seidler U, de Weerth A, Dignass AU, Herfarth H, Reinshagen M, Schreiber S, Junge U, Schrott M, Stein J. (2005) Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease–a randomized, controlled, open-label, multicentre study. American Journal of Gastroenterology 100:2503–2509.				
Affiliation/Source of funds				
There was no conflict of interest for any of the authors. This study was sponsored by Vifor Int., St. Gallen, Switzerland. Additional support came from the Else Kroner-Fresenius Foundation.				
Study design	Level of evidence		Location/setting	
RCT	II		Germany	
Intervention	Comparator			
IV iron – single 7 mg/kg body weight dose, followed by five 200 mg infusions for the following 5 weeks.	Oral iron 100 to 200 mg/day for 6 weeks			
Population characteristics				
Patients with IBD and iron deficiency anaemia (Hb ≤ 1.05 g/L for females and Hb ≤ 1.10 g/L for males; TSAT ≤20% and/or serum ferritin concentrations ≤20 µg/L).				
Length of follow-up	Outcomes measured			
6 weeks	Functional/performance status			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	22		24	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	18		17	
Safety analysis	NR		NR	
Outcome	IV iorn n/N (%) Mean ± SD (N)	Oral iron n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Median (range) CDAI [Crohn's Disease activity index) at baseline N=29	217 (46 to 417)	281 (71 to 423)	NR	NR

Median (range) CDAI at follow-up N=29	74 (23 to 279)	78 (0 to 353)	NR	NR
Median (range) CAI [colitis activity index] at baseline N=17	11 (7 to 19)	8 (4 to 11)	NR	NR
Median (range) CAI at follow-up N=17	5 (1 to 9)	3 (0 to 5)	NR	NR
Median (range) SF-36 score at baseline N=NR	104.5 (95.0 to 113.5)	111.0 (105.0 to 116.5)	NR	NR
Median (range) SF-36 score at follow-up N=NR	108.0 (100.0 to 116.5)	116.0 (108.0 to 120.0)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to IBD patients with iron deficiency anaemia				
Applicability				
Mostly applicable to the Aus context.				
Comments				

STUDY DETAILS: RCT		
Citation		
Ferrini PR, Grossi A, Vannucchi AM, Barosi G, Guarnone R, Piva N, Musto P, and Balleari E. (1998) A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. British Journal of Haematology 103:1070–1074.		
Affiliation/Source of funds		
Not disclosed		
Study design	Level of evidence	Location/setting
RCT	II	Italy
Intervention	Comparator	
rHuEPO (150 U/kg/d) for 8 weeks	Placebo for 8 weeks	
Population characteristics		
Patients with low-risk MDS, as defined according to the presence of bone marrow blasts (RA, RARS, RAEB with bone marrow blast cells < 10%).		
Length of follow-up	Outcomes measured	

8 weeks (for the double-blind phase)		RBC transfusion incidence, stroke		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	44		43	
Efficacy analysis (ITT)	44		43	
Efficacy analysis (PP)	38		37	
Safety analysis	NR		NR	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
RBC transfusion incidence	Although the percentage of transfused patients was lower in the EPO arm than in the placebo one, the difference was not statistically significant.			
Stroke, n/N (%)	1/44 (2.3)	0/43 (0.0)		
EXTERNAL VALIDITY				
Generalisability				
The study is somewhat generalisable to patients with MDS				
Applicability				
The study is somewhat applicable to the Australian context				
Comments				

STUDY DETAILS: RCT		
Citation		
Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, Paietta E, Van Der Jagt R, Houston J, Thomas ML, Cella D, and Rowe JM. (2009) Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: Results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). Blood 114:2393–2400.		
Affiliation/Source of funds		
This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, Chair) and the Canadian Leukemia Studies Group (R.v.d.J., Chair), supported in part by Public Health Service grants (CA23318, CA66636, CA21115, CA80775, CA07190, CA11083, CA17145, CA13650) from the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services.		
Study design	Level of evidence	Location/setting
RCT	II	Multicentre (North America and Israel)

Intervention	Comparator
Daily SC EPO with or without G-CSF SC EPO 150 U/kg daily for 4 months. For non-responders, G-CSF (1 µg/kg/day) was added. Patients who did not respond after addition of G-CSF received increased EPO doses (300 U/kg/day plus G-CSF. Erythroid responders were scheduled to remain on their effective treatment for 1 year. For haematocrit increases to more than 40 vol% (haemoglobin 13 g/dL), EPO was withheld and restarted at decreased frequency when the haematocrit decreased to less than 32 vol%. G-CSF doses were incrementally adjusted based on the absolute neutrophils count.	Patients crossed over to SC EPO after 4 months if there was absence of erythroid response.
Population characteristics	
Adults with myelodysplastic syndrome Patients with the following myelodysplastic syndrome subtypes were eligible for enrolment: refractory anaemia, refractory anaemia with ring sideroblasts (RARS), refractory anaemia with excess blasts (RAEB), or non-proliferative chronic myelomonocytic leukemia according to the French-American-British (FAB) group criteria. Patients were required to have pretreatment bone marrow blasts less than 10% and peripheral blasts less than 5%. Thus, eligible persons included RAEB-1 but not RAEB-2 patients, as classified by World Health Organization (WHO) criteria.23Ahematocrit of less than 30 vol% or hemoglobin less than 9.5 g/dL, a platelet count of more than 30 000/cmm, and documentation of adequate iron stores, were required at the time of enrollment and at each treatment step.	
Length of follow-up	Outcomes measured
1 year QOL- 4 months	Survival, quality of life, adverse events
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Poor	
RESULTS	

Population analysed	Intervention	Comparator
Randomised	Not clear	Not clear
Efficacy analysis (ITT)	53	57
Efficacy analysis (PP)	53	57
Safety analysis	53	57

QOL analysis (baseline)	49		53	
QOL analysis (4 months)	42		42	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Overall survival	38/53 (71.7)	48/57 (84.2)	HR 0.77 (0.48, 1.24)	P=0.28
Overall survival (male)	25/33 (75.8)	33/36 (91.7)	HR 0.63 (0.34, 1.17)	P=0.14
Overall survival (female)	13/20 (65.0)	15/21 (71.4)	HR 0.77 (0.28, 2.14)	P=0.62
Overall survival (age<65 years)	5/10 (50.0)	4/7 (57.1)	HR 1.00 (0.13, 7.51)	P=1.00
Overall survival (RA MDS) [refractory anaemia]	14/20 (70.0)	17/22 (77.3)	HR 0.84 (0.40, 1.80)	P=0.66
Overall survival (RARS MDS) [refractory anaemia with ring sideroblasts]	12/20 (60.0)	15/17 (88.2)	HR 0.41 (0.18, 0.96)	P=0.041
Overall survival (RAEB MDS) [refractory anaemia with excess blasts]	11/12 (91.7)	15/17 (88.2)	HR 1.54 (0.55, 4.33)	P=0.41
Overall survival (patients with no previous transfusion support)	14/21 (66.7)	14/21 (66.7)	HR 0.72 (0.31, 1.64)	P=0.43
Overall survival (patients with previous transfusion support)	24/32 (75.0)	33/35 (94.3)	HR 0.67 (0.36, 1.26)	P=0.22
Overall survival (EPO<200 mU/mL)	25/38 (65.8)	31/38 (81.6)	HR 0.71 (0.39, 1.28)	P=0.25
Overall survival (EPO≥200 mU/mL)	13/15 (86.7)	16/18 (88.9)	HR 0.87 (0.37, 2.02)	P=0.74

Overall survival (lower risk IPSS score) [International Prognostic Scoring System: takes into account age, white blood cell count, haemoglobin levels, peripheral blood blast percentage and constitutional symptoms]	29/43 (67.4)	41/48 (85.4)	HR 0.73 (0.43, 1.25)	P=0.25
Overall survival (higher risk IPSS score) [see above]	9/9 (100.0)	7/9 (77.8)	HR 1.46 (0.12, 17.08)	P=0.76
FACT [functional assessment of cancer therapy] subscale and fatigue scores (at 4 months follow-up)	NR	NR	NR	P>0.05
FACT score (patients who had an erythroid response at 4 months)	Significant improvement from baseline in physical (P=0.007), emotional (P=0.02), and functional (P=0.005) well-being, as well as fatigue (P=0.02) and overall QOL (P=0.02; 2-way analysis of variance)			
Congestive heart failure (grade 3), n/N (%)	1/57 (1.8)	0/53 (0.0)	NR	NR
DVT, n/N (%)	1/57 (1.8)	0/53 (0.0)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients with MDS.				
Applicability				
The study is mostly applicable to the Australian context.				
Comments				

STUDY DETAILS: RCT
Citation
Thompson JA, Gilliland DG, Prchal JT, Bennett JM, Larholt K, Nelson RA, Rose EH, and Dugan MH. (2000) Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. Blood 95:1175–1179.

Affiliation/Source of funds				
From the Division of Oncology, University of Washington, Seattle, WA; Hematology/Oncology Research, Howard Hughes Medical Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Division of Hematology/Oncology, University of Alabama, Birmingham, AL; Cancer Center, University of Rochester, Rochester, NY; RW Johnson Pharmaceutical Research Institute, Raritan, NJ; and Schering Plough Research Institute, Kenilworth, NJ.				
Study design	Level of evidence		Location/setting	
RCT	II		USA	
Intervention	Comparator			
GM-CSF plus EPO	GM-CSF plus placebo			
Population characteristics				
Patients with a diagnosis of MDS and RA, RARS, or RAEB.				
Length of follow-up	Outcomes measured			
12 weeks	RBC transfusion, stroke mortality			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Poor				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	45		21	
Efficacy analysis (ITT)	45		21	
Efficacy analysis (PP)	45		21	
Safety analysis	NR		NR	
Outcome	EPO + GM-CSF n/N (%) Mean ± SD (N)	GM-CSF + placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
RBC transfusion incidence, n/N (%)	34/45 (76)	19/21 (90)		
RBC transfusion incidence (baseline endogenous EPO ≤ 500 mU/mL), n/N (%)	15/25 (60)	11/12 (92)		
RBC transfusion incidence (baseline endogenous EPO > 500), n/N (%)	19/20 (95)	8/9 (89)		

Mean (SD) units of RBC transfused during Months 2 and 3	7.6 (NR)	9.1 (NR)	NR	NR
Mean (SD) units of RBC transfused during Months 2 and 3 (baseline endogenous EPO ≤ 500 mU/mL)	5.9 (NR)	9.5 (NR)	NR	P=0.09
Mean (SD) units of RBC transfused during Months 2 and 3 (baseline endogenous EPO > 500)	9.7 (NR)	8.6 (NR)	NR	P=0.62
Stroke, n/N (%)	1/45 (2.2)	0/21 (0.0)		
Mortality, n/N (%)	3/45 (6.7)	0/21 (0.0)		
EXTERNAL VALIDITY				
Generalisability				
The study is somewhat generalisable to patients with MDS				
Applicability				
The study is mostly applicable to the Australian context.				
Comments				

F4 Evidence summary – Question 4

Fresh frozen plasma

Level II evidence

STUDY DETAILS: RCT		
Citation		
Leese T, Holliday M, Heath D, Hall AW, Bell PR. Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis. Br J Surg 1987;74:907–11		
Affiliation/Source of funds		
The work was funded by a locally organised research grant from Trent Regional Health Authority (UK)		
Study design	Level of evidence	Location/setting
RCT	Level II	Leicester Royal Infirmary, Glenfield General Hospital, Petersborough District Hospital and the George Eliot Hospital, Nuneaton (UK).
Intervention	Comparator	
FFP 2 units daily for 3 days (total 400 ml/day)	400 ml daily of human albumin solution as colloid control.	
Population characteristics		
Patients with severe acute pancreatitis and no coagulopathy. The nine Glasgow criteria for predicting severity in acute pancreatitis were recorded after diagnosis. The presence of 3 or more of these adverse criteria predicts a severe attack of pancreatitis. Twelve patients were entered into the trial more than once, accounting for a total of 30 attacks of acute pancreatitis. These attacks, which were not associated with mortality, were equally randomised to the two treatment groups. Patients in the two study groups were equally matched in predicted severity, prognostic score, age, aetiology of pancreatitis, history of prior pancreatitis, and other clinical parameters.		
Length of follow-up	Outcomes measured	
105 days	Death Median hospital stay Serum α_1 –antiprotease concentration Serum α_2 –macroglobulin concentration Major complications	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: 202 patients presenting with acute pancreatitis were randomised to receive FFP (2 units daily for 3 days) or a similar volume of colloid control as part of their intravenous fluid therapy. One patient refused to be randomised after informed consent and 2 patients with mild alcoholic pancreatitis were randomised in error as their serum amylase was <1000 units/ml. This left 198 patients in the study who were equally randomised to the intervention and comparator groups. No differences in a range of clinical and laboratory outcome measures were reported.		
RESULTS		

Population analysed	FFP		Albumin	
Randomised	99		99	
Efficacy analysis (ITT)	99		99	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	FFP n/N (%)	Albumin n/N (%)	Risk estimate (95% CI) [a]	Significance P-value [a]
Death	8/99 (8)	9/99 (9)	0.89 (0.36–2.21)	*No significant benefit* P=0.80
Gastrointestinal haemorrhage	1/99	4/99	0.25 (0.03–2.2)	*No significant benefit* P=0.21
Major complications	14/99	20/99	0.70 (0.38–1.3)	*No significant benefit* P=0.26
EXTERNAL VALIDITY				
Generalisability				
Generalisable to adult patients with severe acute pancreatitis.				
Applicability				
Highly applicable to the Australian context, and somewhat applicable to current medical practice (study was published in 1987).				
Comments				
The study was underpowered for all primary outcomes. Difficulties in blinding were likely to be due to the nature of the intervention.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

STUDY DETAILS: RCT		
Citation		
Leese T, Holliday M, Watkins M, Thomas WM, Neoptolemos JP, Hall C, Attard A. A multicentre controlled clinical trial of high-volume fresh frozen plasma therapy in prognostically severe acute pancreatitis. Ann R Coll Surg Engl 1991;73: 207–14.		
Affiliation/Source of funds		
The work was funded by a locally organised research grant from Leicestershire Health Authority		
Study design	Level of evidence	Location/setting
RCT	Level II	The study involved the Leicester Royal Infirmary, Leicester General Hospital, Glenfield General Hospital and Dudley Road Hospital, Birmingham (UK).
Intervention	Comparator	

FFP 8 units daily for 3 days (total 400 ml/day)	2000 ml daily of human albumin solution as colloid control.

Population characteristics

Patients referred during the period 1 June 1987 to 31 May 1989 with a clinical diagnosis of acute pancreatitis and serum amylase >1000 μ/L. Only patients with prognostically severe pancreatitis (three or more adverse Glasgow prognostic criteria) were considered for entry into the trial. The two groups were well matched for age, sex, Glasgow prognostic score and aetiology of pancreatitis, monitoring and other potential treatments received.

Length of follow-up	Outcomes measured
90 days	Death Median hospital stay Major complications Circulating protein concentrations

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Fair

Description: A total of 301 attacks of acute pancreatitis in 276 patients were referred for consideration. Of these, 75 attacks were predicted severe, but three of these patients were not randomised because of late referral, non-availability of albumin and gross congestive cardiac failure contraindicating colloid therapy. Therefore 72 patients were randomised to the study, with 36 to receive FFP and 36 to receive colloid control. One patient was subsequently withdrawn from the FFP group due to an FFP shortage. Two patients were subsequently withdrawn from the colloid control group because of the development of congestive cardiac failure on day 1 and a misdiagnosed perforated duodenal ulcer. This left 35 patients in the FFP group and 34 in the colloid control group.

No differences in a range of clinical and laboratory outcome measures were reported.

RESULTS

Population analysed	FFP		Albumin	
Randomised	36		36	
Efficacy analysis (ITT)	35		34	
Efficacy analysis (PP)	NR		NR	
Safety analysis	35		34	
Outcome	FFP n/N (%)	Albumin n/N (%)	Relative risk (95% CI) [a]	Significance P-value [a]
Death	7/36 (19)	6/36 (17)	1.17 (0.43–3.13)	*No significant benefit* P=0.76
Gastrointestinal haemorrhage	0/36 (0)	1/36 (3)	0.33 (0.01–7.92)	*No significant benefit* P=0.50

EXTERNAL VALIDITY

Generalisability

Generalisable to adult patients with severe acute pancreatitis.

Applicability

Highly applicable to the Australian context, and somewhat applicable to current medical practice (study was published in 1991).
Comments
The study was underpowered for all primary outcomes. Difficulties in blinding were likely to be due to the nature of the intervention.

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

STUDY DETAILS: RCT		
Citation		
Gazzard, B.G., Henderson, J.M. & Williams, R. (1975) Early changes in coagulation following a paracetamol overdose and a controlled trial of fresh frozen plasma therapy. Gut, 16, 617–620.		
Affiliation/Source of funds		
The authors were supported by the King's College Hospital Research Committee and Serological Products Ltd.		
Study design	Level of evidence	Location/setting
RCT (n=20)	Level II	Single site in the UK (Liver Unit, King's College Hospital and Medical School, London)

Intervention	Comparator
FFP 300 ml/6 h (600 ml if prothrombin time ratio > 7)	No FFP (unless prothrombin time ratio > 7)
Population characteristics	
The trial was carried out in 20 consecutive patients who developed severe coagulation defect following paracetamol overdose, as shown by a prothrombin time ratio of more than 2.2. The 20 patients were randomised to supportive therapy only or to treatment with FFP until the prothrombin time ratio had fallen to less than 1.4. The baseline characteristics of patients are presented below. At the time of randomisation, the two groups of patients were similar with respect to prothrombin time ratio, age and dose of paracetamol ingested.	
Length of follow-up	Outcomes measured
7 days from overdose	Mortality Development of severe encephalopathy Prothrombin time ratio at three days Evidence of bleeding
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: The clinical effectiveness of FFP in comparison with a control group given no FFP was assessed in a study population including 20 patients with liver disease due to paracetamol overdosage (as shown by a prothrombin time ratio of more than 2.2). The 20 patients were randomly allocated to supportive therapy only or to treatment with FFP (300ml every 6 hours) until the prothrombin time ratio had fallen to less than 1.4. For both groups, if at any time, the prothrombin time ratio rose to 7.0 or more, the dose of FFP was increased to 600 ml.	
RESULTS	

Population analysed	Intervention	Comparator
Randomised	10	10
Efficacy analysis (ITT)	NR	NR
Efficacy analysis (PP)	NR	NR
Safety analysis	NR	NR

Outcome	FFP n/N (%)	No FFP n/N (%)	Relative Risk (95% CI) [a]	Significance P-value [a]
Mortality	1/10 (10)	2/10 (20)	0.5 (0.1 - 4.7)	*No significant benefit* P=1
Evidence of bleeding	0/10 (0)	0/10 (0)	NA	NA
EXTERNAL VALIDITY				
Generalisability				
Generalisable to adults with coagulation defects and hepatic damage following paracetamol overdose.				
Applicability				
Highly applicable to the Australian context, and somewhat applicable to current medical practice (study was published in 1975).				
Comments				
The small size of the study was not optimal to detect any clinically or statistically significant differences in clinical outcomes between the two groups. Many details about randomisation, allocation of concealment and analysis were not reported.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

[a] Relative risk and p values were not reported, but were calculated separately

Prophylactic platelet transfusion

Level II evidence

STUDY DETAILS: RCT		
Citation		
Solomon J, Bofenkamp T, Fahey JL, Chillar RK, Beutler E, et al. Platelet prophylaxis in acute non-lymphoblastic leukemia. The Lancet 1978;1 (8058):267		
Affiliation/Source of funds		
Not reported		
Study design	Level of evidence	Location/setting
RCT (n=31)	Level II	USA
Intervention	Comparator	
Prophylactic platelet transfusion (when platelet count <20 x 10^9/L with clinically significant bleeding) Platelet dose not stated.	Specifically indicated transfusion (transfusion administered when clinically significant bleeding or platelet count <20 x 10^9/L was preceded by a decline in platelet count of ≥50% in the preceding 24 hours (rescue arm).	
Population characteristics		
Adult patients with acute lymphoblastic leukaemia (excluding promyelotic leukaemia) with thrombocytopenia induced by induction chemotherapy. Previously untreated.		

Length of follow-up	Outcomes measured
One month	Complete remissions Complete and partial remissions All deaths within 1 month/course Bleeding deaths within 1 month/course

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Poor Description: Small poor quality study (published letter).
RESULTS

Population analysed	Intervention		Comparator	
Randomised	17		12	
Efficacy analysis (ITT)	15		12	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Prophylactic platelets n/N (%) Mean ± SD (N)	Specifically indicated platelets n/N (%) Mean ± SD (N)	Relative risk (95% CI)	Significance P-value
Deaths within 1 month	3/17	2/12	1.06 (0.21, 5.40)	*No significant effect* P=0.95
Bleeding deaths within 1 month	2/17	0/2	3.61 (0.19, 69.09)	*No significant effect* P=39

EXTERNAL VALIDITY
Generalisability
Due to the small size of the study, it is of limited generalisability to thrombocytopenic patients with cancer.
Applicability
The study is very old, and therefore of limited applicability to current clinical practice in Australia.
Comments
Platelet trigger for transfusion was 20 x 10^9/L

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Higby DJ, Cohen E, Holland JF, Sinks L. The prophylactic treatment of thrombocytopenic leukemic patients with platelets: a double blind study. Transfusion 1974;14:440–445				
Affiliation/Source of funds				
United States Public Health Service Grants CA-5834 and CA-11987 from the National Cancer Institute				
Study design	Level of evidence		Location/setting	
RCT (n=21)	Level II		US	
Intervention	Comparator			
Prophylactic platelet transfusion (approx 3 x10^{11} platelets / square metre). Platelets given in both arms if septic shock or significant bleeding.	Therapeutic plasma infusion (platelet poor).			
Population characteristics				
Adult afebrile thrombocytopenic patients with acute myelocytic leukaemia, without evidence of bleeding or haemolysis. Significant thrombocytopenia was defined as having a platelet count < 30 x 10^9/L, and the study was terminated if a patient's count increased beyond this level and remained in this range without platelet support.				
Length of follow-up	Outcomes measured			
Intervention: 12 days Comparator: 9 days	Remission rates Number having serious bleeding events during days on study Platelet count increment			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Eighteen patients with thrombocytopenia and acute leukaemia were randomised to receive either platelets or platelet-poor plasma as a prophylaxis against bleeding. Despite no significant differences in platelet counts between patients of the two groups, the frequency of bleeding in the two groups was significantly different. Small poor quality study of questionable applicability to current clinical practice.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	12		9	
Efficacy analysis (ITT)	12		9	
Efficacy analysis (PP)	NR		NR	
Safety analysis	12		9	
Outcome	Platelet transfusion n/N (%)	Plasma transfusion n/N (%)	Relative Risk (95% CI) [a]	Significance P-value

Major bleeding events	3/12	6/9	0.38 (0.13, 1.11)	*Favours intervention* P=0.08
EXTERNAL VALIDITY				
Generalisability				
Given the small size of the study, the results have limited generalisability to the assessed study population.				
Applicability				
Applicable to the Australian context, but only somewhat applicable to current medical practice (study was published in 1975).				
Comments				
The small size of the study was not optimal to detect any clinically or statistically significant differences in clinical outcomes between the two groups. Many details about randomisation, allocation of concealment and analysis were not reported.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

[a] Relative risk and p values were not reported, but were calculated separately

Level III-IV evidence

STUDY DETAILS: Retrospective cohort study		
Citation		
Khorana et al. 2008		
Affiliation/Source of funds		
The study was supported, in part, by grant K23 CA120587 from the National Cancer Institute (Dr Khorana) and by grants R21HL086367 and R01HL078603 from the National Heart, Lung, and Blood Institute (Drs Blumberg and Francis).		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	60 academic medical centres in the USA
Risk factor/s assessed	Potential confounding variables measured	
Various including platelet transfusion	Age, sex, cancer site, race/ethnicity, chemotherapy, venous catheters, transfusions, comorbidities.	
Population characteristics (including size)		
The study population comprised 504 208 hospitalised patients with cancer admitted between 1995 and 2003. More than one-third of the patients were 65 years or older. More than two-thirds of the population was white, with blacks representing 12.3% and Hispanics 4.6%. Venous thromboembolism occurred in 21 040 patients (4.2%), including 17 613 (3.5%) with deep venous thrombosis and 5547 (1.1%) with pulmonary embolism; arterial thromboembolic (ATE) events occurred in 16 651 patients (3.3%).		
Length of follow-up	Outcomes measured	
NR	Venous thromboembolism, Arterial thromboembolism Mortality	
Method of analysis		

Variables associated with a higher risk of thromboembolism were identified using multivariate logistic regression. The fixed set of medically relevant covariates was chosen before analysis. Cancer type was included in the model with all disease categories first. After adjusting for the additional covariates, cancer types associated with an increased risk of VTE were kept as separate categories, and the remaining were grouped into the reference category. The final multivariate analysis included cancer type, age, sex, race/ethnicity, and clinical variables that were statistically significantly associated with risk of event in the full model.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: a retrospective cohort study examining the associations between transfusions and venous thromboembolism, arterial thromboembolism, and mortality in hospitalised patients with cancer, using a large discharge database.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	15,237		488,971	
Analysed	15,237		488,971	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
In-hospital mortality	Platelet transfusion	No platelet transfusion	2.40 (2.27–2.52)	*Platelet transfusion is significantly and independently associated with in-hospital mortality* P<0.001
VTE	Platelet transfusion	No platelet transfusion	1.20 (1.11–1.29)	*Platelet transfusion is significantly and independently associated with VTE* P<0.001
ATE	Platelet transfusion	No platelet transfusion	1.55 (1.40–1.71)	*Platelet transfusion is significantly and independently associated with VTE* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a hospitalised cancer patients				
Applicability				
The results of this study are applicable to the Australian setting				
Comments				
Although this study provides low level (Level III-2) evidence, it is extremely large and well powered to detect rare events such as mortality and thromboembolism. Treatments other than chemotherapy were not reported.				

STUDY DETAILS: Prospective cohort study

Citation				
Slichter et al. 1997				
Affiliation/Source of funds				
The study was supported by grants from the National Heart, Lung, and Blood Institute, National Institutes of Health.				
Study design	Level of evidence		Location/setting	
Prospective cohort study	Level IV		Multiple centres in the USA	
Risk factor/s assessed		Potential confounding variables measured		
Four types of platelet transfusions: unmodified, pooled platelet concentrates from random donors (control); filtered, pooled platelet concentrates from random donors (F-PC); ultraviolet B–irradiated, pooled platelet concentrates from random donors (UVB-PC); or filtered platelets obtained by apheresis from single random donors (F-AP). All patients received transfusions of filtered, leukocyte-reduced red cells.		None		
Population characteristics (including size)				
Patients who were receiving induction chemotherapy for acute myeloid leukemia.				
Length of follow-up		Outcomes measured		
NR		- Alloimmune-mediated refractoriness to platelet transfusions - Positive tests for lymphocytotoxic antibodies or antibodies against platelet glycoproteins. - Safety outcomes		
Method of analysis				
Descriptive statistics				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: A multi-institutional, randomised, blinded trial to determine whether the use of platelets from which leukocytes had been removed by a filter or that had been treated with ultraviolet B irradiation would prevent the formation of antiplatelet alloantibodies and refractoriness to platelet transfusions. The study provides an overall rate of post-transfusion reaction but no comparative data.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	530 patients		N/A	
Analysed	530 patients		N/A	
Outcome (categorical)	Risk factor definition	No risk factor definition	Frequency	Significance P-value
Incidence of severe platelet-transfusion reactions	Platelet transfusion	N/A	160[a] transfusions (2.0%) 114/530 patients (22%)	N/A

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to patients receiving induction chemotherapy for acute myeloid leukemia.
Applicability
It is not clear if the interventions assessed in this study reflect standard of care in Australia.
Comments
The study provides an overall rate of post-transfusion reaction but no comparative data. Results based on the combined outcomes from both treatment arms of an RCT (comparing photochemically treated with conventional platelets). The incidence of transfusion-related adverse events were not stratified by risk factors.

[a] The overall number of transfusions was not reported

STUDY DETAILS: RCT analysed as a case series		
Citation		
McCullough et al. 2004		
Affiliation/Source of funds		
The study was sponsored by Cerus and Baxter		
Study design	Level of evidence	Location/setting
RCT analysed as a prospective cohort study	Level IV	Numerous sites in the USA
Risk factor/s assessed	Potential confounding variables measured	
Platelet transfusion	None	
Population characteristics (including size)		
Patients were eligible for enrolment if they had thrombocytopenia requiring platelet transfusion support and were at least 6 years of age. The underlying diagnoses of participants were: acute leukaemia, chronic leukaemia, lymphoma, myelodysplasia, plasma cell dyscrasia, non-haematopoeitic solid tumour and other. Only 3.4% of patients were aged less than 16.		
Length of follow-up	Outcomes measured	
NR	Patients with grade 2 bleeding according to WHO criteria, on any day during PLT support Patients with grades 3–4 bleeding according to WHO criteria, on any day during PLT support Number of days with grade 2 bleeding according to WHO criteria 1 and 24 hr corrected count increment Safety endpoints Death	
Method of analysis		
Descriptive statistics		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Poor

Description: A transfusion trial of platelets photochemically treated for pathogen inactivation using the synthetic psoralen

amotosalen HCl. Patients with thrombocytopenia were randomly assigned to receive either photochemically treated (PCT)

or conventional (control) platelets for up to 28 days. The primary end point was the proportion of patients with World Health

Organization (WHO) grade 2 bleeding during the period of platelet support.

RESULTS

Population	With risk factor		Without risk factor	
Available	645 patients		N/A	
Analysed	645 patients		N/A	
Outcome (categorical)	Risk factor definition	No risk factor definition	Frequency	Significance P-value
Any grade 2 bleeding	Platelet transfusion	N/A	374/645 cases (58.0%)	N/A
Any grade 3–4 bleeding	Platelet transfusion	N/A	33/645 cases (5.1%)	N/A
Transfusion related adverse events	Platelet transfusion	N/A	180/645 (27.9%)	N/A
Death	Platelet transfusion	N/A	28/645 (4.3%)	N/A

EXTERNAL VALIDITY

Generalisability

The results of this study are generalisable to cancer patients. It should be noted that the study population is includes a small proportion of paediatric patients.

Applicability

The results of this study are applicable to the Australian setting

Comments

The study provides an overall rate of post-transfusion reaction but no comparative data.

Results based on the combined outcomes from both treatment arms of an RCT (comparing photochemically treated with conventional platelets).

Platelet transfusion were given according to each institutions guidelines either prophylacticially to prevent bleeding or therapeutically to treat existing bleeding or prepare for an invasive procedure.

STUDY DETAILS: Prospective cohort study

Citation

Heim et al. 2008

Affiliation/Source of funds

The study was supported in part by a grant of the Swiss National Research Foundation and Oncosuisse.

Study design	Level of evidence	Location/setting
Prospective cohort study	Level IV	Single site in Switzerland

Risk factor/s assessed	Potential confounding variables measured

Platelet transfusion	None
Population characteristics (including size)	
Patients with malignant or nonmalignant hematologic diseases in need of prophylactic or therapeutic PLT transfusions and patients with nonhematologic malignancies being treated with myeloablative chemotherapy or with hematopoietic stem cell transplantation (HSCT). 9923 transfusions were given to 672 patients.	
Length of follow-up	Outcomes measured
NR	Transfusion efficacy (using corrected count increment) Transfusion related adverse reactions
Method of analysis	
Descriptive statistics	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Poor Description: A prospective single-centre study in which 9923 mainly prophylactic PLT transfusions given to 672 patients treated for haematologic malignancies between 1997 and 2004 were investigated. Patient and product factors were analysed. Transfusion efficacy was measured by the corrected count increment (CCI), and side effects were recorded.	
RESULTS	

Population	With risk factor		Without risk factor	
Available	9,923 transfusions in 672 patients		N/A	
Analysed	9,923 transfusions in 672 patients		N/A	
Outcome (categorical)	Risk factor definition	No risk factor definition	Frequency	Significance P-value
Post-transfusion reactions in patients who had no fever before transfusion	Platelet transfusion	N/A	753/9,923 cases (7.5% of all transfusions)	N/A
Fever in patients who had no fever before transfusion	Platelet transfusion	N/A	682/9,923 cases (6.9% of all transfusions)	N/A

EXTERNAL VALIDITY	
Generalisability	
The results of this study are generalisable to a hospitalised cancer patients	
Applicability	
The results of this study are applicable to the Australian setting	
Comments	
The study provides an overall rate of post-transfusion reaction but no comparative data. A standardised questionnaire was introduced in 1997 and attached to each PLT product from the apheresis laboratory of the University hospital asking for information about patient factors and transfusion results. The former included weight and height, diagnosis, main treatment, and the presence or absence of fever at the time of transfusion. The latter asked for PLT counts before transfusion (pretransfusion count) and 15 to 60 minutes after transfusion (postransfusion count). Transfusions were given between 2 and 6 hours after measuring the pretransfusion PLT counts. In addition, side effects occurring during or after transfusion of the PLT product were noted.	

PLT, platelet

STUDY DETAILS: Prospective cohort study				
Citation				
Osselaer et al. 2008				
Affiliation/Source of funds				
The study was supported by research grants from Cerus Corp				
Study design	Level of evidence		Location/setting	
Prospective cohort study	Level IV		Multiple centres in Belgium, Norway, Spain and Italy.	
Risk factor/s assessed		Potential confounding variables measured		
Photochemically treated (INTERCEPT) platelet transfusion		None		
Population characteristics (including size)				
The majority of patients received PLT transfusions in non-intensive care hospital locations; however a substantial number of study PLT components were transfused in intensive care units and a small proportion in outpatient clinics. Hematooncology diseases with or without chemotherapy and/or stem cell transplant constituted 58.1% of the primary diagnoses among the transfused patient population. A significant number of patients receiving PLT transfusion (26.9%) underwent cardiovascular surgery. Other diagnoses included surgical interventions (such as orthopedic, neurologic, obstetric, organ transplant, and multiple trauma). Additional primary indications for PLT transfusions were systemic sepsis due to unspecified sources, gastrointestinal bleeding, and sepsis secondary to localized infections.				
Length of follow-up		Outcomes measured		
NR		Adverse reactions Platelet transfusion related adverse reactions Serious adverse reactions Risk factors associated with transfusion reactions		
Method of analysis				
Descriptive statistics				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Apheresis or buffycoat PLT components were leukoreduced, suspended in approximately 35 percent plasma and 65 percent PLT additive solution, and treated with the INTERCEPT process. Blood centres were requested to complete a safety data form after each transfusion. The study provides an overall rate of post-transfusion reaction but no comparative data.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	5106 transfusions in 651 patients		N/A	
Analysed	5106 transfusions in 651 patients		N/A	
Outcome (categorical)	Risk factor definition	No risk factor definition	Frequency	Significance P-value

Any transfusion related adverse event	Platelet transfusion	N/A	42/5106 transfusions (0.8%) 32/651 patients (4.9%)	N/A
Transfusion related serious adverse event	Platelet transfusion	N/A	1/5106 transfusions (0.2%) 1/651 patients (0.2%)	N/A

EXTERNAL VALIDITY
Generalisability
Given the mix of patients included in this study, the results are only somewhat generalisable to cancer patients.
Applicability
The intervention assessed in the study was photochemically inactivated platelet transfusion (INTERCEPT). It is not clear if this intervention reflects standard of care in Australia.
Comments
The study provides an overall rate of post-transfusion reaction but no comparative data. There was the potential for overreporting due to the absence of a blinded design and the increased awareness among observers that a new type of PLT component was under evaluation. This was partly addressed: at one of the study centres, the researchers compared the prevalence of transfusion associated adverse events rates in this case series with the prospective data collected during an 18-month period before routine implementation of PLT components treated with pathogen inactivation. The researchers found a significant reduction in reactions to treated platelet components, while the incidence of reactions to RBCs was equal in both periods. This suggests that observer sensitivity for overreporting did not occur.

Platelet dose

Level II evidence

STUDY DETAILS: RCT		
Citation		
Slichter, S. J. et al., 2010, Dose of prophylactic platelet transfusions and prevention of hemorrhage: New England Journal of Medicine, v. 362, no. 7, p. 600–613.		
Affiliation/Source of funds		
Supported by the National Heart, Lung, and Blood Institutes		
Study design	Level of evidence	Location/setting
RCT (n=1272)	Level II	A number of sites in the USA
Interventions		
Low dose: 1.1 x10^{11} platelets per square meter per transfusion Medium dose: 2.2 x10^{11} platelets per square meter per transfusion High dose: 4.4 x10^{11} platelets per square meter per transfusion		
Population characteristics		

Patients were eligible for the study if they were inpatients of any age undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumours and it was expected that they would have platelet counts of 10,000 per cubic millimeter or lower for 5 days or more.				
Length of follow-up	Outcomes measured			
The study was considered to be completed at 30 days after the first platelet transfusion, after a 10-day period without a platelet transfusion, at hospital discharge, at death, or at withdrawal from the study — whichever occurred first.	Bleeding of WHO grade 2 or higher Serious adverse events Highest grade of bleeding during the study Platelet transfusions RBC transfusions			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: a trial of prophylactic platelet transfusions to evaluate the effect of platelet dose on bleeding in patients with hypoproliferative thrombocytopenia.				
RESULTS				
Population analysed	Low dose	Medium dose	High dose	
Randomised	417	423	432	
Efficacy analysis (ITT)	417	423	432	
Efficacy analysis (PP)	NR	NR	NR	
Safety analysis	417	423	432	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Significance P-value
Death from haemorrhage (low dose vs medium dose)	0/417 (0)	0/423 (0)	NE	NE
Death from haemorrhage (medium dose vs high dose)	0/423 (0)	1/432(0)	0.34 (0.01, 8.33)	*No significant effect* P=0.51
Death from haemorrhage (low dose vs high dose)	0/417 (0)	1/432 (0)	0.35 (0.01, 8.45)	*No significant effect* P=0.51
≥1 Episode of bleeding of grade 2 or higher (low dose vs medium dose)	71/417 (17)	69/423 (16)	1.04 (0.77, 1.41)	*No significant effect* P=0.78
≥1 Episode of bleeding of grade 2 or higher (medium dose vs high dose)	69/423 (16)	70/432 (16)	1.01 (0.74, 1.36)	*No significant effect* P=0.97

≥1 Episode of bleeding of grade 2 or higher (low dose vs high dose)	71/417 (17)	70/432 (16)	1.05 (0.78, 1.42)	*No significant effect* P=0.75
Serious adverse events (low dose vs medium dose)	35/417 (8)	27/423 (6)	1.31 (0.81, 2.13)	*No significant effect* P=0.27
Serious adverse events (medium dose vs high dose)	27/423 (6)	36/432 (8)	0.77 (0.47, 1.24)	*No significant effect* P=0.28
Serious adverse events (low dose vs high dose)	35/417 (8)	36/432 (8)	1.01 (0.65, 1.57)	*No significant effect* P=0.97
Adverse event occurring during or ≤4 hr after a transfusion (low dose vs medium dose)	193/417 (46)	181/423 (43)	1.08 (0.93, 1.26)	*No significant effect* P=0.31
Adverse event occurring during or ≤4 hr after a transfusion (medium dose vs high dose)	181/423 (43)	205/432 (47)	0.90 (0.78, 1.05)	*No significant effect* P=0.17
Adverse event occurring during or ≤4 hr after a transfusion (low dose vs high dose)	193/417 (46)	205/432 (47)	0.98 (0.85, 1.13)	*No significant effect* P=0.73
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to inpatients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumours. It should be noted that the population was not restricted to adults; however the baseline demographics suggest that the majority of patients were adults.				
Applicability				
The results of this study were applicable to current Australian clinical practice.				
Comments				
Low doses of platelets administered as a prophylactic transfusion led to a decreased number of platelets transfused per patient but an increased number of transfusions given.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT
Citation
Heddle, N. M. et al., 2009, A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia: Blood, v. 113, no. 7, p. 1564–1573.

Affiliation/Source of funds				
The study was funded by the BEST collaborative.				
Study design	Level of evidence		Location/setting	
RCT (n=129)	Level II		Six academic teaching hospitals participated in the study: 3 Canadian sites, 1 Norwegian site, and 2 sites in the United States.	
Intervention	Comparator			
Standard dose prophylactic platelet transfusion (3–6 x 10^{11} platelets/product)	Low dose prophylactic platelet transfusion (1.5–3 x 10^{11} platelets/product)			
Population characteristics				
The study included adults with chemotherapy-induced thrombocytopenia requiring prophylactic platelet transfusion. The population included patients with acute leukaemia, chronic leukaemia, lymphoma, and non-haematopoietic solid tumours.				
Length of follow-up	Outcomes measured			
Data on the indication for platelet transfusions and signs and symptoms of bleeding were collected daily during each patient's period of thrombocytopenia. The last day was defined as the day of one or more of the following: 30 days of follow-up; patient withdrawal; death; or the day of the last platelet transfusion before marrow recovery.	Occurrence of a WHO grade 2 or higher bleed Frequency of individual grades of bleeding Time to first bleed Recurrent event analysis to determine the mean number of bleeding days over time per 100 patients Duration of thrombocytopenia Platelet transfusion requirements RBC transfusion requirements Interval between platelet transfusions			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: STOP was a multicenter prospective RCT done in association with the BEST collaborative using study sites in Canada, Norway and the US. Patients were eligible if they were thrombocytopenic and were likely to require at least 6 prophylactic platelet transfusions during their period of chemotherapy-induced thrombocytopenia.				
RESULTS				
Population analysed	Standard dose		Low dose	
Randomised	61		58	
Efficacy analysis (ITT)	61		58	
Efficacy analysis (PP)	NR		NR	
Safety analysis	61		58	
Outcome	Standard dose n/N (%)	Low dose n/N (%)	Risk estimate (95% CI)	Significance P-value

Occurrence of a WHO grade 2 or higher bleed	30/61 (49.2)	30/58 (51.7)	0.95 (0.67, 1.36)	*No significant effect* P=0.78
EXTERNAL VALIDITY				
Generalisability				
This study is generalisable to patients with chemotherapy-induced thrombocytopenia.				
Applicability				
The results are applicable to current Australian clinical practice.				
Comments				
A pre-established safety threshold indicated that the study should be stopped by the DSMB if the cumulative incidence of Grade 4 bleeding exceeded an absolute difference of 5% between the two study arms at any time after 50 patients had been enrolled into each treatment arm. The DSMB stopped the study in March 2008, based on this stopping rule, after enrollment of a total of 130 patients.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT		
Citation		
Tinmouth A, Tannock IF, Crump M, et al. Low-dose prophylactic platelet transfusions in recipients of an autologous peripheral blood progenitor cell transplant and patients with acute leukemia: a randomized controlled trial with a sequential Bayesian design. Transfusion 2004; 44: 1711–9.		
Affiliation/Source of funds		
Canadian Blood Services Grant		
Study design	Level of evidence	Location/setting
RCT (n=111)	Level II	Canada
Intervention	Comparator	
Low dose platelets (3 whole-blood derived platelet units) Exact number of platelets not reported.	Standard dose (5 whole-blood derived platelet units) Exact number of platelets not reported.	
Population characteristics		
Patients undergoing autologous PBPC transplantation or induction chemotherapy for acute myelogenous leukaemia or acute lymphoblastic leukaemia. Patients were excluded if they had acute promyelocytic leukemia, had active bleeding or had abnormal coagulation tests. Platelet transfusions were ordered if the platelet count was <10 x 10^9/L.		
Length of follow-up	Outcomes measured	
Patients remained on the transfusion protocol until one of the following endpoints was reached: recovery of the PLT count , a major bleeding event as determined by the treating physician, refractoriness to random-donor PLT transfusions, discharge from hospital, transfer to an intensive care unit, administration of further chemotherapy, failure of PBPCs to engraft by 30 days, or death.	Bleeding complications Platelet utilisation	

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Patients with acute leukemia or undergoing autologous PBPB transplantation were randomly assigned to receive low-dose (3 PLT units) or standard-dose (5 PLT units) prophylactic PLT transfusions and were monitored daily for bleeding. Using a sequential Bayesian design, the difference in major bleeding events was determined.				
RESULTS				
Population analysed	Low dose		Standard dose	
Randomised	56		55	
Efficacy analysis (ITT)	56		55	
Efficacy analysis (PP)	NR		NR	
Safety analysis	56		55	
Outcome	Low dose n/N (%)	Standard dose n/N (%)	Risk estimate (95% CI)	Significance P-value
Patients with major bleeds				
All patients	6/56 (10.7)	4/55 (7.3)	1.47 (0.44, 4.94)	*No significant effect* P=0.53
Acute leukaemia	4/17 (23.5)	4/17 (23.5)	1.00 (0.30, 3.36)	*No significant effect* P=1.00
Autologous PBPC transplant	2/39 (5.1)	0/38 (0)	4.88 (0.24, 98.32)	*No significant effect* P=0.3
Patients with minor bleeds				
All patients	11/56 (19.6)	22/55 (40.0)	0.49 (0.26, 0.91)	Favours low dose P=0.02
Acute leukaemia	6/17 (35.3)	13/17 (76.5)	0.46 (0.23, 0.93)	Favours low dose P=0.03
Autologous PBPC transplant	5/39 (12.8)	9/38 (23.7)	0.54 (0.20, 1.47)	Favours low dose P=0.23
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients with acute leukaemia, or undergoing autologous PBPC transplantation.				
Applicability				
The study results are probably applicable to the Australian setting.				
Comments				
The study involved a non-traditional Bayesian design. The study was limited by the fact that investigators were not blinded to treatment and the lack of data on the number of platelets transfused.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Goodnough LT, Kuter DJ, McCullough J, et al. Prophylactic platelet transfusions from healthy apheresis platelet donors undergoing treatment with thrombopoietin. Blood 2001; 98: 1346–51.		
Affiliation/Source of funds		
Supported by Amgen, Thousand Oaks, CA		
Study design	Level of evidence	Location/setting
RCT (n=120)	Level II	Five centres in the USA
Interventions		
Platelets derived from donors treated with placebo, PEG-rHuMGDF 1 mg/kg and PEG-rHuMGDF 3 mg/kg. Platelet concentrates (measured at the time of collection) contained a median of: – 3.4×10^{11} platelets for the placebo – 5.7×10^{11} platelets for the PEG-rHuMGDF 1 mg/kg – 11.0×10^{11} platelets for the PEG-rHuMGDF 3 mg/kg		
Population characteristics		
Patients with chemotherapy induced thrombocytopenia (platelet count < 25×10^9/L). Includes patients with breast cancer, acute leukaemia, chronic leukaemia and lymphoma.		
Length of follow-up	Outcomes measured	
7 days	Transfusion related adverse events Other adverse events Platelet count increments Time to next prophylactic platelet transfusion Effect of platelet count increment on bleeding events	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: A study was conducted to determine whether platelets harvested from healthy donors treated with thrombopoietin could provide larger increases in platelet counts and thereby delay time to next platelet transfusion compared to routinely available platelets given to thrombocytopenic patients.		
RESULTS		

Population analysed	Placebo	PEG-rHuMGDF 1 mg/kg	PEG-rHuMGDF 3 mg/kg
Randomised	59 patients received 83 transfusions	15 patients received 18 transfusions	46 patients received 65 transfusions
Efficacy analysis (ITT)	59	15	46
Efficacy analysis (PP)	NR	NR	NR
Safety analysis	59	15	46

Outcome	Placebo n/N (%)	PEG-rHuMGDF 1 mg/kg n/N (%)	PEG-rHuMGDF 3 mg/kg n/N (%)	Relative risk (95% CI)	Significance P-value
Febrile transfusion reaction	7/83 (8.4)	14/83 (16.9)		0.50 (0.21, 1.18)	*No significant effect* P=0.11
Afebrile transfusion reaction	3/59 (5.1)	6/61 (9.8)		0.52 (0.14, 1.97)	*No significant effect* P=0.33
EXTERNAL VALIDITY					
Generalisability					
The study is generalisable to patients with chemotherapy-induced thrombocytopenia.					
Applicability					
The study is applicable to current Australian clinical practice.					
Comments					
-					

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT		
Citation		
Sensebé L, Giraudeau B, Bardiaux L, et al. The efficiency of transfusing high doses of platelets in hematologic patients with thrombocytopenia: results of a prospective, randomized, open, blinded end point (PROBE) study. Blood 2005; 105:862–4.		
Affiliation/Source of funds		
Supported by a grant from Etablissement Francais du Sang		
Study design	Level of evidence	Location/setting
RCT (n=96)	Level II	France
Intervention	Comparator	
Single dose (target 0.5 x 10^{11}/10 kg)	Double dose (target 1.0 x 10^{11}/10 kg)	
Population characteristics		
Patients who had not undergone transfusion who had acute leukaemia undergoing first-line treatment or autologous hematopoietic stem cell transplantation without criteria impairing platelet efficiency.		
Length of follow-up	Outcomes measured	
Patients were followed from the first platelet transfusion until they were discharged and had a stable platelet count more than 25 x 10^9/L or died.	Time between the first and second transfusion Corrected count increment Number of transfusions Number of transfused platelets Bleeding complications	

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: A prospective, randomised, open, blinded end point (PROBE) study to assess the efficiency of transfusing high doses of platelets in patients with thrombocytopenia, either acute leukemia (AL) or those undergoing autologous hematopoietic stem cell transplantation (AT).				
RESULTS				
Population analysed	Single dose		Double dose	
	Acute leukaemia	Autologous transplant	Acute leukaemia	Autologous transplant
Randomised	17	33	14	37
Efficacy analysis (ITT)	17	31	12	36
Efficacy analysis (PP)	NR	NR	NR	NR
Safety analysis	17	31	12	36
Outcome	Single dose n/N (%)	Double dose n/N (%)	Relative risk (95% CI)	Significance P-value
Incidence of haemorrhage	5/50	9/51	0.57 (0.20, 1.57)	No significant effect P=0.28
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients with acute leukaemia or undergoing autologous transplant.				
Applicability				
The study is generally applicable to current Australian clinical practice.				
Comments				
There was no blinding of subjects. Study included patients with acute leukaemia and autologous transplant patients, however the numbers of each group were small and probably underpowered.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

F5 Evidence summary – Question 5

Platelet count and prophylactic platelet transfusion

Level II evidence

STUDY DETAILS: Randomised controlled trial		
Citation		
Rebulla, P., G. Finazzi, F. Marangoni, G. Avvisati, L. Gugliotta, G. Tognoni, T. Barbui, F. Mandelli, and G. Sirchia, 1997, The threshold for prophylactic platelet transfusion in adults with acute myeloid leukemia: New England Journal of Medicine, v. 337, no. 26, p. 1870–1875.		
Affiliaton/Source of funds		
Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA)		
Study design	Level of evidence	Location/setting
RCT N=255	Level II	21 haematology centres in Italy

Intervention	Comparator
Patients who were enrolled in the restrictive protocol received platelet transfusions when the platelet count, which was usually measured in the morning with an automated counter, was below 10,000/mm^3 or was 10,000 to 20,000/mm^3 when the body temperature exceeded 38°C, in the presence of fresh minor or major bleeding, or if invasive procedures were necessary.	Patients in the control group were treated according to the current practice of transfusing platelets prophylactically when the platelet count falls below 20,000 per mm^3.
Population characteristics	
Patients with a diagnosis of acute myeloid leukaemia, hospital admission for the first course of induction chemotherapy, and aged between 16 and 70 years. Patients were excluded if they had acute promyelocytic leukaemia or secondary acute myeloid leukaemia or if they had received a blood transfusion before the diagnosis of acute myeloid leukaemia.	
Length of follow-up	Outcomes measured
100 days	Frequency and severity of haemorrhage Numbers of platelet and red-cell transfusions Rates of complete remission Mortality rates
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Good Description: RCT evaluating the frequency and types of haemorrhage in adolescents and adults with newly diagnosed acute myeloid leukaemia who were undergoing induction chemotherapy and who received platelet transfusions either when the platelet count was 20,000/m^3 or according to a more restrictive protocol.	
RESULTS	

Population analysed	Intervention	Comparator

Randomised	144		132	
Efficacy analysis (ITT)	144		132	
Efficacy analysis (PP)	135		120	
Safety analysis	144		132	
Outcome	10,000/mm^3 n/N (%) Mean ± SD (N)	20,000/mm^3 n/N (%) Mean ± SD (N)	Relative risk (95% CI) Mean difference (95% CI)	Significance P-value
Death	18/144 (13)	9/132 (7)	1.83 (0.85, 3.94)	*No significant difference* P=0.12
Patients with major bleeding episodes	29/144 (20)	24/132 (18)	1.11 (0.68, 1.80)	*No significant difference* P=0.68
Number of RBC units transfused	9.57± 5.18 (135)	9.07± 4.58 (120)	0.50 (-0.70, 1.70)	*No significant difference* P=0.41
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to patients with acute myeloid leukaemia undergoing their first course of induction chemotherapy. Note that the study population includes some adolescents.				
Applicability				
The study is generally applicable to the Australian healthcare setting.				
Comments				
Therapeutic transfusions for bleeding were allowed in both arms, independently of platelet count, but details of the definition of a therapeutic transfusion were not provided. Very few protocol violations compared with other studies of platelet triggers.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: Randomised controlled trial		
Citation		
Heckman, K. D., G. J. Weiner, C. S. Davis, R. G. Strauss, M. P. Jones, and C. P. Burns, 1997, Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000/(mu)L versus 20,000/(mu)L: Journal of Clinical Oncology, v. 15, no. 3, p. 1143–1149.		
Affiliaton/Source of funds		
Supported by the Iowa Leukaemia and Cancer Research Fund, the Dr Richard O. Emmons Memorial Fund, the Mamie C. Hopkins Fund, and the L. McGilliard-T. Johannes Memorial Fund.		
Study design	Level of evidence	Location/setting
RCT (N=78)	Level II	Single site in the USA

Intervention	Comparator
Platelet transfusion threshold of <10 x 10^9/L Platelets given if serious or life-threatening bleeding and for procedures at discretion of physician. Serious or life-threatening bleeding not further defined.	Platelet transfusion threshold of <20 x 10^9/L Platelets given if serious or life-threatening bleeding and for procedures at discretion of physician. Serious or life-threatening bleeding not further defined.
Population characteristics	
Adults more than 17 years of age who were receiving induction for acute leukaemia, mainly myeloid, either newly presenting or in relapse	
Length of follow-up	Outcomes measured
24 days (median)	Survival (at time of analysis) Remission rates (time period not stated) Bleeding episodes per patient Transfusion requirements (platelets, red cells) Hospital stay Adverse events
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: An RCT comparing two prophylactic platelet transfusion thresholds in patients undergoing induction therapy for acute leukemia. Seventy-eight patients undergoing induction therapy for acute leukemia were randomized to receive prophylactic apheresis platelet concentrates at two transfusion thresholds. There was no significant difference in the total number of bleeding episodes per patient, RBC transfusion requirements, febrile days, days hospitalized, days thrombocytopenic, need for HLA-matched platelets, remission rate, or death during induction chemotherapy. No patient in either group died from haemorrhage or underwent major surgery for bleeding complications.	

RESULTS				
Population analysed	10 x 10^9/L trigger		20 x 10^9/L trigger	
Randomised	37		41	
Efficacy analysis (ITT)	37		41	
Efficacy analysis (PP)	NR		NR	
Safety analysis	37		41	
Outcome	10 x 10^9/L trigger n/N (%) Mean ± SD (N)	20 x 10^9/L trigger n/N (%) Mean ± SD (N)	Relative Risk (95% CI) Mean difference (95% CI)	Significance P-value
Mortality	25/37 (68)	29/41 (71)	0.96 (0.71, 1.29)	*No significant difference* P=0.76
Mortality from bleeding	0/37 (0)	0/41 (0)	NE	NE

Mean RBC transfusions	12.2 ± 6.9 (37)	10.7 ± 5.1 (41)	1.5 (-1.22, 4.22)	*No significant difference* P=0.28
EXTERNAL VALIDITY				
Generalisability				
The results are generalisable to patients receiving induction for acute leukaemia, mainly myeloid, either newly presenting or in relapse.				
Applicability				
The study is relatively old and unlikely to reflect standard clinical practice in Australia.				
Comments				
What constituted a life-threatening bleed was an issue of potential importance given the lack of blinding. No patient in either group died from haemorrhage or underwent major surgery as a result of bleeding complications, meaning that the study was underpowered to detect differences in these outcomes. The study reported a high rate of protocol deviations for the use of platelet transfusions: 38% and 15% of patients in the intervention and control arms respectively. The authors state that these violations were generally minor.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT		
Citation		
Diedrich, B., M. Remberger, A. Shanwell, B. M. Svahn, and O. Ringden, 2005, A prospective randomized trial of a prophylactic platelet transfusionOKA trigger of 10 null 10^9 per L versus 30 null 10^9 per L in allogeneic hematopoietic progenitor cell transplant recipients: Transfusion, v. 45, no. 7, p. 1064–1072.		
Affiliaton/Source of funds		
Supported by grants from the Swedish Cancer Society, the Children's Cancer Foundation, the Swedish Medical Research Council, the Swedish Foundation for Medical Research, the Swedish Society of Medicine, the Cancer Society in Stockholm and the Tobias Foundation.		
Study design	Level of evidence	Location/setting
RCT (N=166)	Level II	Huddinge University Hospital, Sweden
Intervention	Comparator	
Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L	Prophylactic platelet transfusions when morning platelet counts decreased to below 30 x 10^9/L	
Population characteristics		
Patients undergoing allogeneic haematopoietic progenitor cell transplantation (HPCT). Patients with a known bleeding disorder or coagulopathy were excluded. Includes patients with non-malignant disorders (n=4), acute leukaemia (n=47), chronic leukaemia (n=20) and other malignancies (n=8).		

Length of follow-up	Outcomes measured
30 days (retrospectively prolonged to 60 days for number of platelet units transfused and number of days to the last platelet transfusion). Survival and relapse were measured at 3 years.	Time to engraftment of WBCs and ANC Number of RBC transfusions (units) Number of platelet units transfused Number of days to the last platelet transfusion Type of bleeding (WHO grades) Bacteremia Graft vs host disease Hospital stay Death/survival Cost

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Fair

Description: A randomised prospective study in allogeneic HPCT recipients to evaluate the consequence of stringent prophylactic platelet transfusion therapy. No significant differences in clinical outcomes or total number of RBC transfusions were noted between study arms. The incidence and type of bleeding in study groups were also similar. The number of platelet units transfused was significantly lower in patients for whom the transfusion trigger was 10 x 10^9 platelets/L

RESULTS

Population analysed	10 x 10^9/L trigger		30 x 10^9/L trigger	
Randomised	87		79	
Efficacy analysis (ITT)	87		79	
Efficacy analysis (PP)	NR		NR	
Safety analysis	87		79	
Outcome	10 x 10^9/L trigger n/N (%) Mean (range)	30 x 10^9/L trigger n/N (%) Mean (range)	Risk estimate (95% CI)	Significance P-value
Survival (3 years)	59/79 (75)	61/87 (70)	NR	*No significant difference*
Bleeding (WHO Grades 2–4)	14/79 (18)	13/87 (15)	NR	*No significant difference*
Subsequent RBC transfusion (30 days)	4 (0–26)	4 (0–31)	NR	*No significant difference*
Subsequent RBC transfusion (60 days)	5 (0–40)	6 (0–44)	NR	*No significant difference*
Median cost (USD) during first 2 months (range)	$1,600 ($0-$22,400)	$4,000 ($0-$32,400)	NR	NR

EXTERNAL VALIDITY
Generalisability
The results are generalisable to patients undergoing HPCT.
Applicability
The results are applicable to an Australian healthcare setting, although it should be noted that approximately 30% of the study participants were children (aged < 18 years).
Comments
Note that platelets were occasionally transfused at higher platelet count than what was designed for, when a patient had a bleeding event. In patients with WHO Grade 2 bleeding, violations of the protocol occurred in 3 out of 11 patients in the group with a trigger of 10 x 10^9 platelets/L, and in 2 out of 8 patients in the group with a trigger of 30 x 10^9 platelets/L.

HPCT, haematopoietic progenitor cell transplantation; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RCT, randomised controlled trial

STUDY DETAILS: RCT		
Citation		
Zumberg, M. S., M. L. del-Rosario, C. F. Nejame, B. H. Pollock, L. Garzarella, K. J. Kao, R. Lottenberg, and J. R. Wingard, 2002, A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplant recipients: 10,000/L versus 20,000/microL trigger: Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, v. 8, p. 569–576.		
Affiliaton/Source of funds		
Grant from Shands Hospital, the University of Florida		
Study design	Level of evidence	Location/setting
RCT (N=159)	Level II	Shands Hospital, Florida, USA
Intervention	Comparator	
Prophylactic platelet transfusions if morning platelet counts fell below 10 x 10^9/L. If the morning platelet count ranged between 10 to 15 x10^9/L, a platelet count was checked 12 hours later and platelet transfusion was given if the count fell below 10 x 10^9/L.	Prophylactic platelet transfusions if morning platelet counts fell below 20 x 10^9/L	
Population characteristics		
Patients older than 2 years who underwent an allogeneic, matched unrelated donor (MUD), syngeneic, or autologous bone marrow transplant (BMT). Patients were excluded if they had a known bleeding disorder or coagulopathy, concurrent need for anticoagulation, history of acute haemorrhage within 1 week of enrollment or within 1 week of a fall in the platelet count to below 50 x 10^9/L, history of prior bladder irradiation if the use of cyclophosphamide was planned, or platelet alloimmunisation. Includes patients with leukaemia, lymphoma, myeloma and solid tumours.		

Length of follow-up	Outcomes measured
100 days	Number of platelet units transfused Acute bleeding Maximum bleeding score (based on modified GIMEMA criteria) Causes of bleeding Mortality Bleeding days per patient Number of inpatient hospital days

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Poor

Description: Prospective randomised clinical trial in haematopoietic stem cell transplant recipients (HSCT), who received a prophylactic platelet transfusion when the morning platelet count fell below a 10 x 10^9/L or 10 x 10^9/L threshold. Subsequent prophylactic transfusions were administered according to a predetermined algorithm. The number of prophylactic and therapeutic transfusions and the incidence of minor and major bleeding were compared between the 2 groups. A platelet transfusion trigger of 10 x 10^9/L was found to be safe; however, a decrease in platelet use was not achieved.

RESULTS

Population analysed	10 x 10^9/L trigger		20 x 10^9/L trigger	
Randomised	78		81	
Efficacy analysis (ITT)	78		81	
Efficacy analysis (PP)	NR		NR	
Safety analysis	78		81	
Outcome	10 x 10^9/L trigger n/N (%) Mean (N)	20 x 10^9/L trigger n/N (%) Mean (N)	Risk estimate (95% CI)	Significance P-value
Mortality (note that none of the deaths were attributable to bleeding)	8/78 (10)	5/81 (6)	NR	*No significant difference*
Major bleeding events	11/78 (14)	14/81 (17)	NR	*No significant difference*
Number of bleeding days per patient	11.4 (78)	11.4 (81)	NR	*No significant difference* P=0.99
Mean number of packed RBC transfusions	6.0 (78)	5.9 (81)	NR	*No significant difference* P=0.93

EXTERNAL VALIDITY
Generalisability
The results are generalisable to patients undergoing bone marrow or peripheral blood stem cell transplantation. It should be noted that the trial population included some children; however the exact numbers were not provided.
Applicability
The results are generally applicable to the Australian setting; however it should be noted that the patterns of haematopoietic stem cell transplantation may have changed since the trial was undertaken, with fewer autologous transplantations for breast cancer and a larger number of nonmyeloblative transplantations.
Comments
The mean platelet count in patients with a trigger of 20 x 10^9/L was higher at baseline than it was for the group of patients with a trigger of 20 x 10^9/L. It was not reported if this differences was significant. It should also be noted that 49% of the transfusions in the lower trigger arm and 21% of transfusions in the higher trigger arm were given above the assigned trigger level. There was no difference between the two arms in maximum bleeding scores (P = .66). The causes of bleeding were similar for the 2 groups and were primarily mucocutaneous and genitourinary.

GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

Different INR (or PT/aPTT) levels

Level II evidence

STUDY DETAILS: Cohort study		
Citation		
Garden OJ, Motyl, H, Gilmour WH, Utley RJ and Carter DC (1985) Prediction of outcome following acute variceal haemorrhage. British Journal of Surgery 72: 91–95		
Affiliation/Source of funds		
University Department of Surgery, Glasgow Royal Infirmary		
Study design	Level of evidence	Location/setting
Prospective observational study	Level II	Single site in Scotland
Risk factor/s assessed	Potential confounding variables measured	
Various, including prothrombin ratio	Prothrombin ratio, age, sex, cause and duration of liver disease, time since first variceal haemorrhage, presence of ascites, encephalopathy, bilirubin, alanine aminotransferase, alkaline phosphatase, urea, creatinine, total protein, kaolin cephalin clotting ratio, thrombin ratio, haemoglobin, white cell count, platelet count.	
Population characteristics (including size)		
Patients with acute variceal haemorrhage N=70 (100 admissions)		
Length of follow-up	Outcomes measured	
NR	Survival	

Method of analysis			
Student's t and Mann-Whitney tests for independent samples of data were used to determine the significance of differences between the group of patients who died and those who were discharged in terms of mean value for each factor. χ^2 analysis was used to evaluate whether categorical variables could predict outcome. Stepwise logistic regression analysis was used to minimise the number of admission factors needed for optimum separation of patients who survived from those who died.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: In order to identify factors predicting survival following acute variceal haemorrhage, data were collected prospectively from 100 admissions in 70 patients. Of the ten predictive factors identified by univariate analysis, only prothrombin ratio, serum creatinine and the presence of encephalopathy on admission were shown by stepwise logistic regression to have independent significance. The derived regression equation allowed clearer identification than conventional scoring systems of high and low risk groups and successfully predicted outcome in 90% of admissions.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	NR		
Analysed	NR		
Outcome (categorical)	Risk factor definition	Risk estimate (95% CI)	Significance P-value
Absolute prothrombin ratio	Absolute prothrombin ratio (the study does not report different prothrombin time thresholds)	The prothrombin ratio at admission is an independent predictor of admission mortality. P<0.001	
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to patients with acute variceal haemorrhage. For the majority of patients, variceal bleeding was caused by cirrhosis or hepatitis.			
Applicability			
The study is relatively old, and is therefore likely to have limited applicability to current standard of care in Australia.			
Comments			
It should also be noted that the study did not stratify patients by different prothrombin time thresholds, but rather reported the association between absolute prothrombin ratio and admission mortality.			

STUDY DETAILS: Cohort study
Citation
Violi, F. et al., 1995, Prognostic value of clotting and fibrinolytic systems in a follow-up of 165 liver cirrhotic patients: Hepatology, v. 22, no. 1, p. 96–100.
Affiliation/Source of funds
Andrea Cesalpino Foundation, Italy

Study design	Level of evidence	Location/setting
Prospective observational study	Level II	Single site in Italy

Risk factor/s assessed	Potential confounding variables measured
Various, including fibrinogen, prothrombin activity, aPTT	Favtor VII, prekallikrein, grade of liver disease, D-dimer, albumin, bilirubin, age.

Population characteristics (including size)

Patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure. Patients were excluded if they had hepatocarcinoma, spontaneous bacterial peritonitis or other infectious disease or cholestatic liver diseases. In the case of immediate need for blood or plasma, coagulation study was performed before transfusion.

N=165

Length of follow-up	Outcomes measured
2 years	Survival

Method of analysis

Univariate analysis of survival was performed with the log rank test. A total of 10 variables were considered. For continuous variables the quartiles Q1 and Q3 were chosen as indicators. The variables that achieved statistical significance (P < .05) in the univariate analysis were subsequently included in a multivariate analysis using a Cox regression. Age was always forced in the model.

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Poor

Description: In the univariate analysis, fibrinogen, aPTT and prothrombin activity were associated with survival; however, only two variables, prekallikrein and factor VII activity were significantly associated with survival in the multivariate analysis.

RESULTS

Population	With risk factor	Without risk factor	
Available			
Analysed			
Outcome (categorical)	Risk factor definition	Risk estimate (95% CI)	Significance P-value
Fibrinogen	>254 mg/dL, 254–196 mg/dL,195–143 mg/dL, <143 mg/dL	In the univariate analysis, fibrinogen, aPTT and prothrombin activity were associated with survival; however, only two variables, prekallikrein and factor VII activity were significantly associated with survival in the multivariate analysis.	
aPPT	<1.3 mg/dL, 2.0–3.4 mg/dL, 1.3–1.9 mg/dL, >3.4 mg/dL		
Prothrombin activity	<28 sec, 28–30 sec, 31–36 sec,>36 sec		

EXTERNAL VALIDITY

Generalisability

The results of this study are generalisable to cirrhotic patients with different degrees of liver failure.

Applicability

The results are moderately applicable to the Australian healthcare setting.

Comments

Note that the purpose of the study was to identify factors to predict which patients were better candidates for liver transplantation. In the univariate analysis, fibrinogen, aPTT and prothrombin activity were not associated with survival. Therefore these prognostic factors were not included in the multivariate analysis.

STUDY DETAILS: Cohort study

Citation

Nallamothu, B. K. et al., 2005, Prognostic implication of activated partial thromboplastin time after reteplase or half-dose reteplase plus abciximab: Results from the GUSTO-V trial: European Heart Journal, v. 26, no. 15, p. 1506–1512.

Affiliation/Source of funds

The GUSTO-V study was sponsored by Centocor (Malvern, PA, USA) and Eli Lilly (Indianapolis, IA, USA). The investigator was supported as a clinical scholar by a K-12 grant from the National Institutes of Health (RR017607–01).

Study design	Level of evidence	Location/setting
Cohort analysis of RCT data	Level II	820 hospitals in 20 countries (including Australia)

Risk factor/s assessed	Potential confounding variables measured
Peak activated partial thromboplastin time (aPTT) levels	Non-linear relationships were explored using cubic spline functions, and then appropriate linear spline functions were used in the models. For moderate-to-severe bleeding, intracerebral haemorrhage, and reinfarction, the analyses were adjusted for age, gender, and weight. In the analysis of 30-day mortality, we adjusted for age and gender, and also included other covariates such as previous myocardial infarction, the use of nitrates in <48 h, blood pressure, pulse, Killip classification, infarct location, and time to reperfusion therapy in the final model. Interaction terms were included in the models to determine whether the associations varied between treatment groups.

Population characteristics (including size)

The GUSTO-V trial enrolled 16,588 patients in the first 6 h of evolving ST-segment elevation myocardial infarction were randomly assigned standard-dose reteplase or half-dose reteplase and full-dose abciximab. Reteplase is an anti fibrinolytic, and abciximab is an antiplatelet agent. Both study arms were also treated with intravenous unfractionated heparin (UFH). A lower dose of UFH in the combination therapy group was used to compensate for the anticoagulant effect of abciximab. For these analyses, patients were also excluded if they: (i) received low molecular weight heparin at any point during their hospitalisation (n=4,627), (ii) did not receive UFH (n=66), or (iii) had no peak aPTT level measured (n=475). Therefore, the final population included in the current analysis consisted of 11,420 patients.

Length of follow-up	Outcomes measured
The primary endpoint of GUSTO-V was overall 30-day mortality. Additional endpoints assessed at 7 days or discharge (whichever occurred first) included moderate to severe bleeding, intracerebral haemorrhage, and reinfarction.	Severe bleeding, intracerebral haemorrhage, reinfarction, and 30-day mortality.

Method of analysis

Univariate comparisons between groups of patients stratified by treatment assignment and peak aPTT levels (<50, 50–70, >70 s) were performed using non-parametric Kruskal–Wallis equality tests and χ^2 tests. Logistic regression was used to model the association between peak aPTT levels and moderate-to-severe bleeding, intracerebral haemorrhage, reinfarction, and 30-day mortality.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Large prospective cohort analysis based on RCT data. The RCT results suggest that combination of half-dose reteplase and abciximab does not lead to a significant reduction in mortality compared with full-dose reteplase alone in the GUSTO V trial. Some secondary endpoints were significantly reduced with the combination; however the combination intervention was also associated with an increase in bleeding.			
RESULTS			
Population	Reteplase + abciximab	Standard dose reteplase	
Available	5,775	5,645	
Analysed	5,775	5,645	
Outcome (categorical)	Risk factor definition	Odds ratio (95% CI)	Significance P-value
30-day mortality (<50 s)	Patients were stratified by treatment assignment and peak aPTT levels (<50, 50–70, >70 s)	0.94 (0.92–0.91) for each 1 s increase in peak aPTT <50 s when compared with a peak aPTT level of 50 s.	*In patients with peak aPTT levels <50 s, increased aPTT levels are associated with a decreased risk of mortality.* P<0.001
30-day mortality (50–70 s)		NR	*There is no association between peak aPTT levels and mortality risk at 30 days, for patients with peak aPTT levels 50–70 s* P=0.461
30-day mortality (>70 s)		NR	*There is no association between peak aPTT levels and mortality risk at 30 days, for patients with peak aPTT levels 50–70 s* P=0.260

Moderate-to-severe bleeding (>70 s)	Patients were stratified by treatment assignment and peak aPTT levels (<50, 50–70, >70 s)	NR	*In patients with peak aPTT levels >70 s, increased aPTT levels are associated with an increased risk of moderate-to-severe bleeding. The risk is greater in patients receiving combination therapy.* P<0.001 (combination therapy) P<0.004 (reteplase therapy)
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to patients receiving anitplatelet and/or antifibrinolytic therapy for ACS. It should be noted that the results may be confounded by greater use of UFH in patients receiving reteplase only.			
Applicability			
The results are applicable to the Australian healthcare setting.			
Comments			
The combination therapy group had a higher percentage of patients with hypertension and hyperlipidaemia. Peak aPTT values were higher (median, 87.3 vs. 66.0 s; P = 0.001) and more rapidly reached (median, 7.2 vs. 19.3 h; P = 0.001) in patients receiving standard-dose reteplase compared with combination therapy. It remains unclear as to why bleeding rates would be higher in patients with lower aPTT levels in the combination therapy group. This is most likely due to the observational nature of the data. Patients that develop early bleeding complications are very likely to have their UFH discontinued rapidly resulting in low peak aPTT levels. It should also be noted that the correlations observed are based on peak aPTT levels, and may have been different had aPTT levels been assessed at specific time points. Overall, there is an increased risk of moderate-to-severe bleeding and death at 30 days for patients with aPTTs over 70 s.			

Level III evidence

STUDY DETAILS: Retrospective cohort study		
Citation		
Le Moine, O. et al., 1992, Factors related to early mortality in cirrhotic patients bleeding from varices and treated by urgent sclerotherapy: Gut, v. 33, no. 10, p. 1381–1385.		
Affiliation/Source of funds		
Not reported		
Study design	Level of evidence	Location/setting
Retrospective cohort study (N=102)	Level III-3	Single site in Belgium
Risk factor/s assessed	Potential confounding variables measured	

Various (including prothrombin time)	Qualitative variables include: sex, aetiology of cirrhosis, activity of alcoholism, duration of liver disease from initial diagnosis, degree of ascites, degree of encephalopathy, extra-hepatic infection, previous non-surgical haemostatic procedures before admission if referred from other hospitals, source of variceal bleeding, staging of oesophageal varices and presence of blood in stomach. The quantitative variables include: age, systolic blood pressure, heart rate, haemoglobin, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin, the number of blood units transfused within 72 hours of admission, the amount of polidocanol injected per patient during the first sclerotherapy session, Chile-Pugh score, and serum creatinin.
Population characteristics (including size)	
Patients with a diagnosis of parenchymal cirrhosis confirmed by pertinent clinical, biochemical or histological data. All had oesophageal varices at endoscopy. Cirrhosis was of alcoholic origin in 62% of the cases. When admitted to hospital, all patients were managed by fluid resuscitation followed by endoscopy and mixed intravariceal and paravariceal sclerotherapy. Follow up sclerotherapy was always done after 48 hours unless recurrent bleeding occurred earlier and then at 1–2 weeks' interval during the same hospital stay.	
Length of follow-up	Outcomes measured
6 weeks	Survival or death as a result of liver failure or exsanguination
Method of analysis	
Survival curves were analysed using the actuarial method of Mantel-Haenzel. Statistical analysis was performed on the 91 patients still alive after 72 hours and after exclusion of the patients dying from causes other than liver failure and exsanguinations (N=8). Two stepwise logistic regression procedures were performed. The first using the Pugh score alone as an independent variable, and the second including all variables achieving statistical significance ($P<0.1$) in univariate analysis using χ^2 tests. Variables were then entered into or removed from the logistic regression equation one at a time.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Good Description: 121 patients with their first variceal bleeding episode between June 1983 and December 1988 were retrospectively studied. Nineteen patients were excluded. Insufficient data on survival or incomplete medical records excluded 7 other patients, and 12 patients were not studied because of prehepatic portal hypertension. Two of the 12 qualitative variables and 7 of the thirteen quantitative variables in the univariate analysis influenced survival at 6	

RESULTS				
Population	With risk factor		Without risk factor	
Available	102			
Analysed	102			
Outcome (categorical)	Risk factor definition	No risk factor definition	Regression coefficient (SE)	Significance P-value

Mortality related to liver disease	Prothrombin time (absolute value in %)	0.102 (0.037)	*The value of the prothrombin time at admission is associated with mortality related to liver disease.* P<0.01
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of community-dwelling disabled women aged ≥ 65 years.			
Applicability			
The study is poorly applicable to the current Australian healthcare setting.			
Comments			
The study does not report different prothrombin time thresholds. Therefore it does not provide useful information about the identification of a trigger for plasma transfusion.			

STUDY DETAILS: Cohort study		
Citation		
Krige JEJ, Kotze UK, Distiller G, Shaw J and Bornman PC (2009) Predictive factors for rebleeding and death in alcoholic cirrhotic patients with acute variceal bleeding: a multivariate analysis. World Journal of Surgery 33:2127–2135		
Affiliation/Source of funds		
Not reported		
Study design	Level of evidence	Location/setting
Retrospective cohort study	III-3	Single site in Belgium
Risk factor/s assessed	Potential confounding variables measured	
Various, including INR	Tested variables included albumin level (<25 vs.>25 g/l), total bilirubin level (<51 vs. >51 lmol/l), ascites (nil and mild vs. moderate and severe), and encephalopathy (nil and mild vs. moderate and severe). The categorical variables included gender, age (<60 years vs.>60 years), pitressin, and theneed for balloon tube tamponade.	
Population characteristics (including size)		
Adult patients with endoscopically proven acute esophageal variceal bleeding from alcohol-related cirrhosis who were treated with injection sclerotherapy. (N=310).		
Length of follow-up	Outcomes measured	
6 weeks	6-week variceal rebleeding rate Death	
Method of analysis		
The Mann Whitney test for independent variables was used for group comparison. Multivariate analysis was performed according to a logistic regression model.		

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Retrospective cohort study including 792 patients, out of which 67 patients (8.5%) were lost to follow-up. The study found that female gender (relative risk (RR) = 5.234, P<0.001), acute promyelocytic leukemia (RR=4.057, P=0.003), leukocytosis (RR=3.301, P=0.004), thrombocytopenia (RR=3.283, P=0.005) and prolonged prothrombin time (RR=3.291, P=0.016) were significantly associated with occurrence of FICH in multivariate analysis.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR			
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
Mortality	INR ≥2.3	INR ≤2.3	4.93 (1.70, 14.24)	An INR ≥2.3 is significantly associated with an increased risk of death P=0.003
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to patients with esophageal variceal bleeding from alcohol-related cirrhosis				
Applicability				
The results are moderately applicable to the Australian healthcare setting.				
Comments				
Although the study was published relatively recently, it should be noted that the analysis included data collected from patients over a 26 year period. Results from older patients may have limited applicability to the current Australian healthcare setting.				

STUDY DETAILS: Cohort study		
Citation		
Kim, H., J. H. Lee, S. J. Choi, J. H. Lee, M. Seol, Y. S. Lee, W. K. Kim, J. S. Lee, and K. H. Lee, 2006, Risk score model for fatal intracranial hemorrhage in acute leukemia: Leukemia, v. 20, no. 5, p. 770–776.		
Affiliation/Source of funds		
Not reported		
Study design	Level of evidence	Location/setting
Retrospective cohort study	III-3	Asan Medical Centre, Seoul, Korea
Risk factor/s assessed	Potential confounding variables measured	

Various, including the following: • plasma fibrinogen: < 250 vs ≥ 250 mg/dl • Prothrombin time (PT): <1.5 vs ≥ 1.5 INR • Activated partial thromboplastim time (aPTT): < 48 vs ≥ 48 s	APL vs acute leukemia other than APL, hemorrhage score (0 vs ≥ 1), ALL vs non-ALL, gender (male vs female), age (< 40 vs ≥ 40 years), white blood cell (WBC) counts (< 50 000 vs ≥ 50 000/mm^3), platelets (< 35 000 vs ≥ 35 000/mm3), peripheral blood blasts (< 70 vs ≥ 70%), performance status (< 70 vs ≥ 70%), performance of induction chemotherapy (done vs not done) and presence of fever (none vs present).

Population characteristics (including size)
Patients with leukaemia diagnosed between July 1989 and March 2003 (N=792).

Length of follow-up	Outcomes measured
Median follow up was 45.6 months (range, 0.7–180.6 months).	Overall survival and fatal intracerebral haemorrhage (FICH) free survival.

Method of analysis
For continuous variables, data were given as medians (ranges) and means (standard deviation). Standard error of the mean was used instead of standard deviation when comparing groups. For nominal variables, data were reported as the number (percent) of patients, unless specified otherwise. Continuous variables were dichotomized and coded into binary variables to make various categorical comparisons. The Kaplan–Meier method was use to estimate the probability of OS and FICH-free survival. The log-rank test was used to compare the difference in survival probability between two groups. For FICH-free survival, both the log-rank test and the Tarone–Ware test were used. Univariate analysis of FICH-free survival was performed by the Kaplan–Meier method for each risk factor. Multivariate prognostic analyses and RR were determined by the Cox proportional-hazard models, using all covariates with P < 0.1 by univariate analysis, plus age and gender. P-values were presented by log-rank test, and linear by linear associations were tested by the χ^2 test.

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good Description: Retrospective cohort study including 792 patients, out of which 67 patients (8.5%) were lost to follow-up. The study found that female gender (relative risk (RR) = 5.234, P<0.001), acute promyelocytic leukemia (RR=4.057, P=0.003), leukocytosis (RR=3.301, P=0.004), thrombocytopenia (RR=3.283, P=0.005) and prolonged prothrombin time (RR=3.291, P=0.016) were significantly associated with occurrence of FICH in multivariate analysis.

RESULTS				
Population	With risk factor		Without risk factor	
Available	77		715	
Analysed	77		715	
Outcome (categorical)	Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
Fatal intracranial haemorrhage	INR ≥ 1.5	INR < 1.5	3.29 (1.25–8.67)	*INR is an independent risk factor for fatal intracranial haemorrhage* P=0.016

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to patients with acute leukaemia.
Applicability

The results are moderately applicable to the Australian healthcare setting.
Comments
Good quality study that adjusted for a range of variables in the multivariate analysis.

STUDY DETAILS: Cohort study				
Citation				
Dally N, Hoffman R, Haddad N, Sarig G, Rowe JM, Brenner B. Predictive factors of bleeding and thrombosis during induction therapy in acute promyelocytic leukemia-a single center experience in 34 patients. Thromb Res. 2005;116(2):109–14				
Affiliation/Source of funds				
Not reported				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	III-3		Single site in Israel	
Risk factor/s assessed		Potential confounding variables measured		
Various, including Prothrombin time (PT) partial thromboplastin time (aPTT), fibrinogen level, platelets and white blood cells.		Platelets, white blood celss, prothrombin time and fibrinogen level.		
Population characteristics (including size)				
Patients with acute promyelocytic leukaemia (APL) receiving induction therapy. (N=34).				
Length of follow-up		Outcomes measured		
Not reported		Severe bleeding included any bleeding to vital organs (intracranial bleeding and diffuse alveolar haemorrhage) or significant bleeding necessitating transfusion (severe vaginal bleeding and intra-abdominal haemorrhage).		
Method of analysis				
The Mann Whitney test for independent variables was used for group comparison. Multivariate analysis was performed according to a logistic regression model.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: The study by Dally et al (2005) was a fair quality retrospective study in patients with acute promyelocytic leukaemia (APL) receiving induction therapy. For a rare disease with high mortality, the cohort size is relatively large and well-powered. The outcomes measured included severe haemorrhagic and thrombotic events.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR			
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value

Severe bleeding	PT <60%	PT ≥60% a	2.6 (0.15, 43.5)	Prothrombin time is not an independent risk factor for bleeding complications P=0.505
Severe bleeding	aPTT ≥27 s	aPTT <27 s	NR	Partial thromboplastin time is not an independent risk factor for bleeding complications
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to patients with promyelocytic acute leukaemia.				
Applicability				
The results are moderately applicable to the Australian healthcare setting.				
Comments				
The study by Dally et al (2005) was a fair quality retrospective study in patients with acute promyelocytic leukaemia (APL) receiving induction therapy. For a rare disease with high mortality, the cohort size is relatively large and well-powered. The outcomes measured included severe haemorrhagic and thrombotic events. Severe bleeding included any bleeding to vital organs (intracranial bleeding and diffuse alveolar haemorrhage) or significant bleeding necessitating transfusion (severe vaginal bleeding and intraabdominal haemorrhage).				

Different fibrinogen levels

Level II evidence

STUDY DETAILS: Cohort study			
Citation			
Violi, F. et al., 1995, Prognostic value of clotting and fibrinolytic systems in a follow-up of 165 liver cirrhotic patients: Hepatology, v. 22, no. 1, p. 96–100.			
Affiliation/Source of funds			
Andrea Cesalpino Foundation, Italy			
Study design	Level of evidence	Location/setting	
Prospective observational study	Level II	Single site in Italy	
Risk factor/s assessed		Potential confounding variables measured	
Various, including fibrinogen, prothrombin activity, aPTT		Favtor VII, prekallikrein, grade of liver disease, D-dimer, albumin, bilirubin, age.	
Population characteristics (including size)			
Patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure. Patients were excluded if they had hepatocarcinoma, spontaneous bacterial peritonitis or other infectious disease or cholestatic liver diseases. In the case of immediate need for blood or plasma, coagulation study was performed before transfusion. N=165			
Length of follow-up		Outcomes measured	
2 years		Survival	
Method of analysis			
Univariate analysis of survival was performed with the log rank test. A total of 10 variables were considered. For continuous variables the quartiles Q1 and Q3 were chosen as indicators. The variables that achieved statistical significance (P < .05) in the univariate analysis were subsequently included in a multivariate analysis using a Cox regression. Age was always forced in the model.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: In the univariate analysis, fibrinogen, aPTT and prothrombin activity were associated with survival; however, only two variables, prekallikrein and factor VII activity were significantly associated with survival in the multivariate analysis.			
RESULTS			
Population	With risk factor	Without risk factor	
Available			
Analysed			
Outcome (categorical)	Risk factor definition	Risk estimate (95% CI)	Significance P-value
Fibrinogen	>254 mg/dL, 254–196 mg/dL,195–143 mg/dL, <143 mg/dL	In the univariate analysis, fibrinogen, aPTT and prothrombin activity were associated with survival; however, only two variables, prekallikrein and factor VII activity were	
aPPT	<1.3 mg/dL, 2.0–3.4 mg/dL, 1.3–1.9 mg/dL, >3.4 mg/dL		

Prothrombin activity	<28 sec, 28–30 sec, 31–36 sec,>36 sec	significantly associated with survival in the multivariate analysis.
EXTERNAL VALIDITY		
Generalisability		
The results of this study are generalisable to cirrhotic patients with different degrees of liver failure.		
Applicability		
The results are moderately applicable to the Australian healthcare setting.		
Comments		
Note that the purpose of the study was to identify factors to predict which patients were better candidates for liver transplantation. In the univariate analysis, fibrinogen, aPTT and prothrombin activity were not associated with survival. Therefore these prognostic factors were not included in the multivariate analysis.		

Level III evidence

STUDY DETAILS: Cohort study		
Citation		
Kim, H., J. H. Lee, S. J. Choi, J. H. Lee, M. Seol, Y. S. Lee, W. K. Kim, J. S. Lee, and K. H. Lee, 2006, Risk score model for fatal intracranial hemorrhage in acute leukemia: Leukemia, v. 20, no. 5, p. 770–776.		
Affiliation/Source of funds		
Not reported		
Study design	Level of evidence	Location/setting
Retrospective cohort study	III-3	Asan Medical Centre, Seoul, Korea
Risk factor/s assessed	Potential confounding variables measured	
Various, including the following: • plasma fibrinogen: < 250 vs ≥ 250 mg/dl • Prothrombin time (PT): <1.5 vs ≥ 1.5 INR • Activated partial thromboplastim time (aPTT): < 48 vs ≥ 48 s	APL vs acute leukemia other than APL, hemorrhage score (0 vs ≥ 1), ALL vs non-ALL, gender (male vs female), age (< 40 vs ≥ 40 years), white blood cell (WBC) counts (< 50 000 vs ≥ 50 000/mm^3), platelets (< 35 000 vs ≥ 35 000/mm3), peripheral blood blasts (< 70 vs ≥ 70%), performance status (< 70 vs ≥ 70%), performance of induction chemotherapy (done vs not done) and presence of fever (none vs present).	
Population characteristics (including size)		
Patients with leukaemia diagnosed between July 1989 and March 2003 (N=792).		
Length of follow-up	Outcomes measured	
Median follow up was 45.6 months (range, 0.7–180.6 months).	Overall survival and fatal intracerebral haemorrhage (FICH) free survival.	

Method of analysis
For continuous variables, data were given as medians (ranges) and means (standard deviation). Standard error of the mean was used instead of standard deviation when comparing groups. For nominal variables, data were reported as the number (percent) of patients, unless specified otherwise. Continuous variables were dichotomized and coded into binary variables to make various categorical comparisons. The Kaplan–Meier method was use to estimate the probability of OS and FICH-free survival. The log-rank test was used to compare the difference in survival probability between two groups. For FICH-free survival, both the log-rank test and the Tarone–Ware test were used. Univariate analysis of FICH-free survival was performed by the Kaplan–Meier method for each risk factor. Multivariate prognostic analyses and RR were determined by the Cox proportional-hazard models, using all covariates with P < 0.1 by univariate analysis, plus age and gender. P-values were presented by log-rank test, and linear by linear associations were tested by the χ^2 test.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Good Description: Retrospective cohort study including 792 patients, out of which 67 patients (8.5%) were lost to follow-up. The study found that female gender (relative risk (RR) = 5.234, P<0.001), acute promyelocytic leukemia (RR=4.057, P=0.003), leukocytosis (RR=3.301, P=0.004), thrombocytopenia (RR=3.283, P=0.005) and prolonged prothrombin time (RR=3.291, P=0.016) were significantly associated with occurrence of FICH in multivariate analysis.
RESULTS

Population	With risk factor		Without risk factor	
Available	77		715	
Analysed	77		715	
Outcome (categorical)	Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
Fatal intracranial haemorrhage	INR ≥ 1.5	INR < 1.5	3.29 (1.25–8.67)	*INR is an independent risk factor for fatal intracranial haemorrhage* P=0.016

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to patients with acute leukaemia.
Applicability
The results are moderately applicable to the Australian healthcare setting.
Comments
Good quality study that adjusted for a range of variables in the multivariate analysis.

STUDY DETAILS: Cohort study
Citation
Dally N, Hoffman R, Haddad N, Sarig G, Rowe JM, Brenner B. Predictive factors of bleeding and thrombosis during induction therapy in acute promyelocytic leukemia-a single center experience in 34 patients. Thromb Res. 2005;116(2):109–14

Affiliation/Source of funds				
Not reported				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	III-3		Single site in Israel	
Risk factor/s assessed		Potential confounding variables measured		
Various, including Prothrombin time (PT) partial thromboplastin time (aPTT), fibrinogen level, platelets and white blood cells.		Platelets, white blood celss, prothrombin time and fibrinogen level.		
Population characteristics (including size)				
Patients with acute promyelocytic leukaemia (APL) receiving induction therapy. (N=34).				
Length of follow-up		Outcomes measured		
Not reported		Severe bleeding included any bleeding to vital organs (intracranial bleeding and diffuse alveolar haemorrhage) or significant bleeding necessitating transfusion (severe vaginal bleeding and intra-abdominal haemorrhage).		
Method of analysis				
The Mann Whitney test for independent variables was used for group comparison. Multivariate analysis was performed according to a logistic regression model.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: The study by Dally et al (2005) was a fair quality retrospective study in patients with acute promyelocytic leukaemia (APL) receiving induction therapy. For a rare disease with high mortality, the cohort size is relatively large and well-powered. The outcomes measured included severe haemorrhagic and thrombotic events.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	NR			
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
Severe bleeding	Fibrinogen <160/mg/dL	Fibrinogen ≥160/mg/dL	1.3 (0.09, 18.8)	Fibrinogen is not an independent risk factor for bleeding complications P=0.843
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to patients with promyelocytic acute leukaemia.				
Applicability				
The results are moderately applicable to the Australian healthcare setting.				
Comments				
Severe bleeding included any bleeding to vital organs (intracranial bleeding and diffuse alveolar haemorrhage) or significant bleeding necessitating transfusion (severe vaginal bleeding and intraabdominal haemorrhage).				

F6 Evidence summary – Question 6

Level II evidence

STUDY DETAILS: Cohort study				
Citation				
Masera G, Terzoli S, Avanzini A (1982) Evaluation of the supertransfusion regimen in homozygous beta-thalassaemia children. Br J Haematol 52(1):111–3.				
Affiliation/Source of funds				
Cattedra di Puericultura, University of Milan, Italy and Laboratorio di Ricerche Cliniche, Istituti Clinici di Perfezionamento, Milan, Italy.				
Study design	Level of evidence		Location/setting	
Prospective cohort study; two study periods: standard transfusion and supertransfusion.	Level II		Outpatient clinic, Milan, Italy	
Risk factor/s assessed		Potential confounding variables measured		
Pre-transfusion Hb		NA		
Population characteristics (including size)				
Total of 11 patients with β-thalassaemia; ages 6–14 years; all patients splenectomised.				
Length of follow-up		Outcomes measured		
Standard transfusion period 4–12 months; supertransfusion period 7–18 months.		Transfusion volume.		
Method of analysis				
Descriptive statistics.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Prospective outpatient clinic based cohort study; data from 11 splenectomised β-thalassaemia patients included; standard transfusion period (mean pre-transfusion Hb 10.2g/dL); supertransfusion period (mean pre-transfusion Hb 12.3g/dL). All patients were transfused regularly every 3–4 weeks and treated with desferrioxamine (40mg/kg/day).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	11			
Analysed	11			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Transfusion volume: (mL/kg/month) (N=32)	Standard transfusion	Supertransfusion (up to 5 months treatment)	Standard transfusion: 16.71±2.0 Supertransfusion: 20.30±3.5	*A standard transfusion regimen results in lower transfusion volume compared to up to 5 months of supertransfusion* P<0.01

Transfusion volume: (mL/kg/month) (N=32)	Standard transfusion	Supertransfusion (more than 5 months treatment)	Standard transfusion: 16.71±2.0 Super transfusion: 16.53±2.0	*A standard transfusion regimen shows no significant difference in transfusion volume compared to over 5 months of supertransfusion.* P=Not significant
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of β-thalasseamia patients aged 6–14 years who have undergone splenectomy.				
Applicability				
This study was conducted at a single centre in Italy. The results are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that the adoption of a super transfusion regimen results in increased blood consumption for five months, after which consumption returns to the same level as with standard transfusion.				

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; kg, kilogram; mg, milligram; mL, millilitre; NR, not reported.

STUDY DETAILS: Cohort study		
Citation		
Torcharus K, Withayathawornwong W, Sriphaisal T, Krutvacho T, Arnutti P, Suwanasophorn C (1993) High transfusion in children with beta-thalassemia/Hb E: clinical and laboratory assessment of 18 cases. Southeast Asian J Trop Med Public Health 24 Suppl 1:96–9.		
Affiliation/Source of funds		
Division of Pediatric Hematology, Pramongkutklao College of Medicine, Banfkok 10400, Thailand.		
Study design	Level of evidence	Location/setting
Prospective, hospital-based cohort	Level II	Hospital, Thailand
Risk factor/s assessed	Potential confounding variables measured	
Pre-transfusion haemoglobin, splenectomised vs. not splenectomised	NA, univariate analysis only.	
Population characteristics (including size)		
Eighteen transfusion-dependent patients with β-thalassaemia or Hb E aged between 2–13 years. Splenomegaly less than 5cm below the left costal margin.		
Length of follow-up	Outcomes measured	
15 months	Transfusion volume.	
Method of analysis		
Descriptive statistics		

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Prospective hospital-based cohort study; data from 18 subjects included; follow up of 15 months. Subjects were regularly transfused and were assigned to one of three treatments regimens: 1. Hyper-transfusion (pre-transfusion Hb >8 g/dL) plus desferrioxamine 500mg 3–5 days per week 2. Hyper-transfusion (pre-transfusion Hb >8 g/dL) 3. Standard transfusion (pre-transfusion Hb 6–7 g/dL)				
RESULTS				
Population	With risk factor		Without risk factor	
Available	18			
Analysed	18			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Transfusion volume (mL/kg/year) (N=3)	Hypertransfusion, desferrioxamine therapy, not splenectomised	Hypertransfusion, desferrioxamine therapy, splenectomised	Not splenectomised: 220±25 Splenectomised: 155±59	*Favours splenectomised subjects* P=NR
Transfusion volume (mL/kg/year) (N=5)	Hyper transfusion	Standard transfusion	Hypertransfusion: 208.4±67 Standard transfusion: 175±45	*A standard transfusion regimen results in lower transfusion volume compared to hyper-transfusion* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of β-thalassaemia patients aged 2–16 years.				
Applicability				
This study was conducted at a single centre in Thailand. The results of this study may be applicable to the Australian setting.				
Comments				
The authors conclude that hyper transfusion with chelation therapy can improve the clinical wee-being of β-thalassaemia patients. The results of the study show that adoption of a hyper-transfusion strategy results in an increase in blood consumption. Additionally, the addition of chelation therapy to hyper-transfusion had no effect on serum ferritin levels.				

AST, aspartate aminotransaminase; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; kg, kilogram; mg, milligram; mL, millilitre; NR, not reported.

Level III evidence

STUDY DETAILS: Cohort study				
Citation				
Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P (1997) A moderate transfusion regimen may reduce iron loading in (beta)-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion 37(2):135–40.				
Affiliation/Source of funds				
Pavia University, Pavia, Italy; IRCCS Policlinico S. Matteo, Pavia, Italy; University of Ferrara, Ferrara, Italy;University of Liège, Liège,Belgium. Funding from Assocaizione Italiana Ricerca sul Cancro, IRCCS Policlinico S. Matteo and Fondazione Ferrata Storti.				
Study design	Level of evidence		Location/setting	
Retrospective crossover cohort study	Level III-2		Department of Paediatrics, University of Pavia, Pavia, Italy.	
Risk factor/s assessed		Potential confounding variables measured		
Pre-transfusion Hb		NA, univariate analysis only.		
Population characteristics (including size)				
Total of 32 patients with β-thalassaemia; transfusion and chelation therapy initiated before end of 1980; no splenectomy between 1981 and 1992; no allogenic bone marrow transplantation; age 16–30 years.				
Length of follow-up		Outcomes measured		
Hyper-transfusion period: 1981–1986, 5 years Moderate transfusion period: 1987–1992, 5 years		Transfusion volume		
Method of analysis				
Descriptive statistics and F test (ANOVA).				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Retrospective crossover observational study of 32 β-thalassaemia patients sequentially treated with two transfusion protocols: hyper-transfusion (pre-transfusion Hb 10–12g/dL, mean 11.3g/dL±0.5) and moderate transfusion (pre-transfusion Hb 9–10g/dL, mean 9.4g/dL±0.4). All patients received regular transfusions as determined by Hb levels and all were treated with desferrioxamine (40–60mg/kg/day).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	32			
Analysed	32			
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Transfusion volume (mean±SD, mL/kg/year) (N=32)	Hyper transfusion	Moderate transfusion	Hyper transfusion: 137±26 Moderate transfusion: 104±23	*A moderate transfusion regimen results in lower transfusion volume compared to hyper-transfusion* P<0.0001

Transfusion volume (mean±SD, mL/kg/year) (N=NR)	Hyper transfusion, splenectomised patients	Moderate transfusion, splenectomised patients	Hyper transfusion: 124±18 Moderate transfusion: 93±14	*A moderate transfusion regimen results in lower transfusion volume compared to hyper-transfusion* P<0.0001
Transfusion volume (mean±SD, mL/kg/year) (N=NR)	Hyper transfusion, not splenectomised patients	Moderate transfusion, not splenectomised patients	Hyper transfusion: 162±21 Moderate transfusion: 126±22	*A moderate transfusion regimen results in lower transfusion volume compared to hyper-transfusion* P<0.0001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of β-thalassaemia patients aged 16–30 years.				
Applicability				
This study was conducted at a single centre in Italy. The results are likely to be applicable to the Australian setting				
Comments				
The authors conclude that the adoption of a moderate transfusion regimen allowed a significant reduction in blood consumption. Additional benefits in the reduction of serum ferritin and acceptable suppression of erythroid proliferation were also achieved with the moderate transfusion regimen.				

ANOVA, analysis of variance; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; IRCCS, Istituto di Ricercae Cura a Carattere Scientifico; kg, kilogram; mg, milligram; mL, millilitre; SD, standard deviation.

STUDY DETAILS: Cohort study		
Citation		
Roudbari M, Soltani-Rad M, Roudbari S. (2008) The survival analysis of beta thalassemia major patients in South East of Iran. Saudi Med J. 29(7):1031–5.		
Affiliation/Source of funds		
Zahedan University of Medical Sciences, Zahedan, Iran and Iran University of Medical Sciences, Tehran, Iran.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Thalassemia Treatment Center, Zahedan, Iran.
Risk factor/s assessed	Potential confounding variables measured	
Pre-transfusion Hb ≤9g/dL	Transfusion frequency, type of blood transfused, serum ferritin, comorbidities.	
Population characteristics (including size)		
Total of 578 patients (333 male) treated at the centre between 1998 and 2006;		
Length of follow-up	Outcomes measured	
NR	Survival	
Method of analysis		
Log rank test and Cox regression model		

INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Retrospective cohort study of 578 β-thalassaemia patients treated with regular transfusions at an Iranian transfusion centre between 1998 and 2006.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	578			
Analysed	147		431	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Survival, years (mean±SE) (N=578)	Pre-transfusion Hb≤9 g/dL	Pre-transfusion Hb>9 g/dL	≤9 g/dL: 26.1±1.56 >9 g/dL: 33.5±2.04	*Favours pre-transfusion Hb >9g/dL* P=0.002
Outcome (continuous)	Continuous measure		Risk estimate (95% CI)	Significance P-value
Survival (N=578)	Pre-transfusion Hb increase of 1g/dL		OR=0.67 (0.47, 0.93)	*A 1 g/dL increase in Hb results in a 33% decrease in the risk of death.* P=0.018
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of β-thalassaemia patients.				
Applicability				
This study was carried out at a single centre in Iran. The results of this study may be applicable to the Australian setting.				
Comments				
The authors conclude that patients with a higher level of Hb have improved survival.				

CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; OR, odds ratio; SE, standard error.

References