Evidence summaries

to support

PICO questions

RBC transfusion triggers

April 2018 (version 3.0)

Centre for Evidence-Based Practice (CEBaP)

Belgian Red Cross

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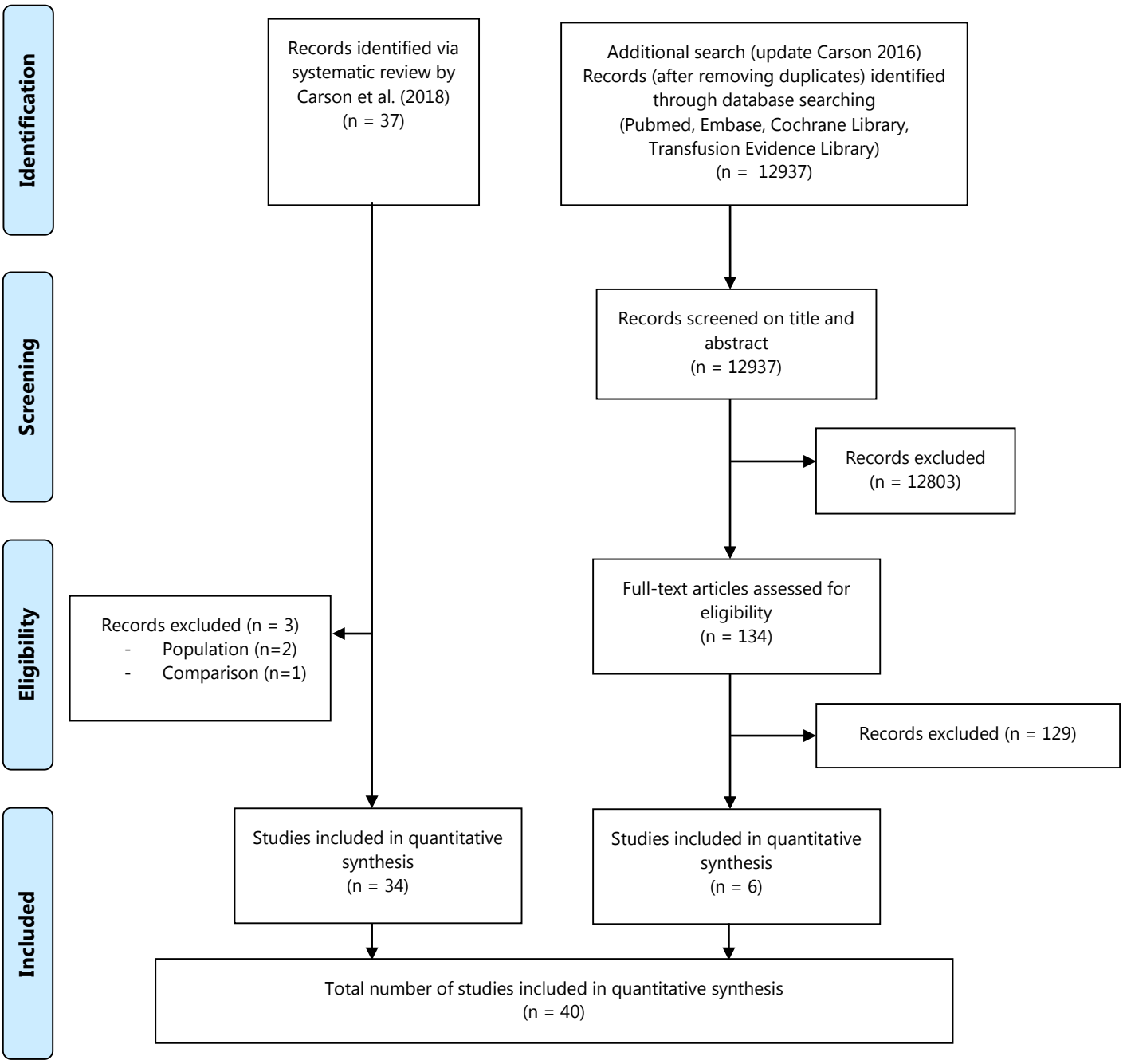
Evidence-based
by CEBaP

Content

Overview responsible methodologists and Scientific Committee members

PICO question #	responsible SC member	responsible methodologist
PICO 4: Adult ICU pts. clinically stable	Erhard Seifried	Anne-Catherine Vanhove
PICO 5: Orthopedic/non-cardiac surgery	Pierre Albaladejo	Anne-Catherine Vanhove
PICO 6: Acute GI bleeding	Giancarlo Liumbruno, Giuseppe Marano, Eva Veropalumbo	Anne-Catherine Vanhove
PICO 7: Symptomatic/acute coronary heart disease	Shubha Allard	Anne-Catherine Vanhove
PICO 8: Septic shock	Erica Wood	Anne-Catherine Vanhove
PICO 9: Cardiac surgery	Jerrold Levy	Anne-Catherine Vanhove
PICO 10: Adult haematological pts.	Pierre Tiberghien	Hans van Remoortel
PICO 11: Adult pts. with solid tumours	Richard Gammon	Hans van Remoortel
PICO 12: Acute CNS injury	Marian van Kraaij	Hans van Remoortel
PICO 13: Cerebral perfusion disorders	Shubha Allard	Hans van Remoortel
PICO 14: Acutely bleeding pts.	Erica Wood, Cecile Aubron	Hans van Remoortel

Flow chart


Identification
Screening
Eligibility
Included
Records identified via systematic review by Carson et al. (2018) (n = 37)
Additional search (update Carson 2016) Records (after removing duplicates) identified through database searching (Pubmed, Embase, Cochrane Library, Transfusion Evidence Library) (n = 12937)
Records screened on title and abstract (n = 12937)
Records excluded (n = 12803)
Full-text articles assessed for eligibility (n = 134)
Records excluded (n = 3)
- Population (n=2)
- Comparison (n=1)
Records excluded (n = 129)
Studies included in quantitative synthesis (n = 34)
Studies included in quantitative synthesis (n = 6)
Total number of studies included in quantitative synthesis (n = 40)

Overview of included studies

PICO question restrictive versus liberal transfusion triggers: population of interest	Included studies from Carson review (2016/2018)[1,2] (34 studies)	Included studies from additional search (6 studies)
1. Critically ill but clinically stable adult intensive care patients	4 studies[3-6]	none
2. Orthopaedic and non-cardiac surgery	11 studies[7-17]	1 study[18]
3. Acute gastrointestinal bleeding*	3 studies[19-21]	none
4. Symptomatic coronary heart disease	2 studies[22,23]	none
5. Septic shock**	2 studies[24,25]	none
6. Cardiac surgery	8 studies[26-33]	none
7. Adult haematological patients	2 studies[34,35]	none
8. Adult patients with solid tumours	1 study[36]	2 studies[37,38]
9. Acute central nervous system injury	none	2 studies[39,40]
10. Cerebral perfusion disorders	none	1 study[41]
11. Acute bleeding patients	1 study[42]	none

* The 3 RCTs in patients with gastrointestinal bleeding were considered as a subgroup of PICO 11 (acute bleeding

** The 2 RCTs in patients with septic shock were considered as a subgroup of PICO 1 (intensive care population)

Reference list included studies

1. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2016;10:CD002042.

2. Carson JL, Stanworth SJ, Alexander JH, et al. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease., 2018.

3. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409-17.

4. Hebert PC, Wells G, Marshall J, et al. Transfusion requirements in critical care. A pilot study. Canadian Critical Care Trials Group. JAMA 1995;273:1439-44.

5. Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Crit Care Med 2013;41:2354-63.

6. Palmieri TL, Holmes JHt, Arnoldo B, et al. Transfusion Requirement in Burn Care Evaluation (TRIBE): A Multicenter Randomized Prospective Trial of Blood Transfusion in Major Burn Injury. Ann Surg 2017;266:595-602.

7. Bush RL, Pevec WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. Am J Surg 1997;174:143-8.

8. Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion 1998;38:522-9.

9. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.

10. Fan YX, Liu FF, Jia M, et al. Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: a preliminary study. Arch Gerontol Geriatr 2014;59:181-5.

11. Foss NB, Kristensen MT, Jensen PS, et al. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. Transfusion 2009;49:227-34.

12. Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: the TRIFE randomized controlled trial. Acta Orthop 2015;86:363-72.

13. Grover M, Talwalkar S, Casbard A, et al. Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. Vox Sang 2006;90:105-12.

14. Lotke PA, Barth P, Garino JP, et al. Predonated autologous blood transfusions after total knee arthroplasty: immediate versus delayed administration. J Arthroplasty 1999;14:647-50.

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16. Parker MJ. Randomised trial of blood transfusion versus a restrictive transfusion policy after hip fracture surgery. Injury 2013;44:1916-8.

17. So-Osman C, Nelissen R, Brand R, et al. The impact of a restrictive transfusion trigger on post-operative complication rate and well-being following elective orthopaedic surgery: a post-hoc analysis of a randomised study. Blood Transfus 2013;11:289-95.

18. Markatou M, Theodoraki K, Rizos D, et al. Targeting perioperative hemoglobin in major abdominal surgery. J Anesthe Clinic Res 2012;3:1-6.

19. Blair SD, Janvrin SB, McCollum CN, et al. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg 1986;73:783-5.

20. Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015;386:137-44.

21. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21.

22. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013;165:964-71 e1.

23. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol 2011;108:1108-11.

24. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.

25. Bergamin FS, Almeida JP, Landoni G, et al. Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. Crit Care Med 2017;45:766-73.

26. Bracey AW, Radovancevic R, Riggs SA, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. Transfusion 1999;39:1070-7.

27. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 2010;304:1559-67.

28. Johnson RG, Thurer RL, Kruskall MS, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg 1992;104:307-14.

29. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015;372:997-1008.

30. Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion 2012;52:91-9.

31. Koch CG, Sessler DI, Mascha EJ, et al. A Randomized Clinical Trial of Red Blood Cell Transfusion Triggers in Cardiac Surgery. Ann Thorac Surg 2017;104:1243-50.

32. Laine A, Niemi T, Schramko A. Transfusion Threshold of Hemoglobin 80 g/L Is Comparable to 100 g/L in Terms of Bleeding in Cardiac Surgery: A Prospective Randomized Study. J Cardiothorac Vasc Anesth 2017.

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34. DeZern AE, Williams K, Zahurak M, et al. Red blood cell transfusion triggers in acute leukemia: a randomized pilot study. Transfusion 2016;56:1750-7.

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36. de Almeida JP, Vincent JL, Galas FR, et al. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. Anesthesiology 2015;122:29-38.

37. Park SH, Nam E, Bang SM, et al. A randomized trial of anemia correction with two different hemoglobin targets in the first-line chemotherapy of advanced gastric cancer. Cancer Chemother Pharmacol 2008;62:1-9.

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39. Ngwenya LB, Suen CG, Tarapore PE, et al. Safety and cost efficiency of a restrictive transfusion protocol in patients with traumatic brain injury. J Neurosurg 2017:1-8.

40. McIntyre LA, Fergusson DA, Hutchison JS, et al. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. Neurocrit Care 2006;5:4-9.

41. Naidech AM, Shaibani A, Garg RK, et al. Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. Neurocrit Care 2010;13:313-20.

42. Fisher MR, Topley E. The illness of trauma. Br J Clin Pract 1956;10:770-6.

PICO 4: RBC transfusion triggers in adult intensive care unit patients, clinically stable

Overview evidence table GRADE software (PICO 4)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
30-day mortality												
6	randomised trials	not serious	not serious	not serious	serious [a]	none	366/1323 (27.7%)	380/1327 (28.6%)	**RR 0.97** (0.82 to 1.15)	**9 fewer per 1.000** (from 43 more to 52 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital mortality												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	263/971 (27.1%)	296/965 (30.7%)	**RR 0.88** (0.76 to 1.02)	**37 fewer per 1.000** (from 6 more to 74 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Participants exposed to blood transfusion												
5	randomised trials	not serious	not serious	not serious	not serious	none	726/1155 (62.9%)	1085/1150 (94.3%)	**RR 0.68** (0.63 to 0.72)	**302 fewer per 1.000** (from 264 fewer to 349 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Units of blood transfused												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [b]	not serious	none	418	420	-	MD **3 units lower** (3.64 lower to 2.36 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Haemoglobin concentration												
3	randomised trials	not serious	not serious	not serious	not serious	none	971	965	-	MD **1.66 lower** (2.15 lower to 1.16 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Cardiac events												
1	randomised trials	serious [c]	not serious	serious [b]	not serious	none	55/418 (13.2%)	88/420 (21.0%)	**RR 0.63** (0.46 to 0.85)	**78 fewer per 1.000** (from 31 fewer to 113 fewer)	⨁⨁◯◯ LOW	CRITICAL
Myocardial infarction												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	49/1057 (4.6%)	42/1058 (4.0%)	**RR 1.01** (0.38 to 2.72)	**0 fewer per 1.000** (from 25 fewer to 68 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Congestive heart failure												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious [c]	not serious	serious [b]	not serious	none	22/418 (5.3%)	45/420 (10.7%)	**RR 0.49** (0.30 to 0.80)	**55 fewer per 1.000** (from 21 fewer to 75 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Sepsis-bacteraemia												
1	randomised trials	serious [c]	not serious	serious [b]	not serious	none	30/418 (7.2%)	40/420 (9.5%)	**RR 0.75** (0.48 to 1.19)	**24 fewer per 1.000** (from 18 more to 50 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Pneumonia												
2	randomised trials	serious [c]	not serious	not serious	serious [a]	none	136/586 (23.2%)	135/597 (22.6%)	**RR 1.03** (0.84 to 1.27)	**7 more per 1.000** (from 36 fewer to 61 more)	⊕⊕◯◯ LOW	IMPORTANT
Pneumonia or wound infection												
1	randomised trials	serious [c]	not serious	not serious	serious [a]	none	42/418 (10.0%)	50/420 (11.9%)	**RR 0.84** (0.57 to 1.24)	**19 fewer per 1.000** (from 29 more to 51 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Number of RBC transfusions												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [c]	not serious	not serious	serious [a]	none	168	171	-	median **8 RBC transfusions lower** (0 to 0)	⨁⨁◯◯ LOW	IMPORTANT
Blood stream infections												
1	randomised trials	serious [d]	not serious	not serious	serious [a]	none	40/168 (23.8%)	42/177 (23.7%)	**RR 1.00** (0.69 to 1.46)	**0 fewer per 1.000** (from 74 fewer to 109 more)	⨁⨁◯◯ LOW	IMPORTANT
Wound infections												
1	randomised trials	serious [d]	not serious	not serious	serious [a]	none	20/168 (11.9%)	21/177 (11.9%)	**RR 1.00** (0.56 to 1.78)	**0 fewer per 1.000** (from 52 fewer to 93 more)	⨁⨁◯◯ LOW	IMPORTANT
Urinary tract infection												
1	randomised trials	serious [d]	not serious	not serious	serious [a]	none	24/168 (14.3%)	24/177 (13.6%)	**RR 1.05** (0.62 to 1.78)	**7 more per 1.000** (from 52 fewer to 106 more)	⨁⨁◯◯ LOW	IMPORTANT
30-day mortality (subgroup: less severe patients (APACHE-score 20 or less))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [c]	not serious	serious [b]	not serious	none	18/207 (8.7%)	35/217 (16.1%)	**RR 0.54** (0.32 to 0.92)	**74 fewer per 1.000** (from 13 fewer to 110 fewer)	⊕⊕◯◯ LOW	CRITICAL
30-day mortality (subgroup: younger patients (<55 years))												
1	randomised trials	serious [c]	not serious	serious [b]	not serious	none	10/173 (5.8%)	21/161 (13.0%)	**RR 0.44** (0.22 to 0.91)	**73 fewer per 1.000** (from 12 fewer to 102 fewer)	⊕⊕◯◯ LOW	CRITICAL
30-day mortality (subgroup: cardiac disease)												
1	randomised trials	serious [c]	not serious	not serious	serious [a]	none	31/151 (20.5%)	40/175 (22.9%)	**RR 0.90** (0.59 to 1.36)	**23 fewer per 1.000** (from 82 more to 94 fewer)	⊕⊕◯◯ LOW	CRITICAL
30-day mortality (subgroup: severe infections and septic shock)												
1	randomised trials	serious [c]	not serious	not serious	serious [a]	none	26/114 (22.8%)	31/104 (29.8%)	**RR 0.77** (0.49 to 1.20)	**69 fewer per 1.000** (from 60 more to 152 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Low number of events and/or large variability of the results; b. Lack of generaliziblity: evidence from 1 Canadian study; c. Detection bias (lack of blinding outcome assessors); d. Detection bias (lack of blinding outcome assessors) - Selection bias (allocation concealment unclear)

Detailed evidence summary (PICO 4)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In critically ill, but clinically stable adult intensive care patients (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. <u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6 **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 **Embase** (via Embase.com interface) using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 **Transfusion evidence library** (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: critically ill but clinically stable adult intensive care patients. Excluded: adult intensive care patients that are not clinically/haemodynamically stable, children or neonates. **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** *Primary*: Mortality (e.g. 30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction,

	congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) (cluster) randomized controlled trials identified in the update. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without haemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Bergamin, 2017, Brazil	Experimental: RCT	300 adult cancer patients with septic shock in the first 6 hours of ICU admission. Restrictive group: n = 151, 84 males and 67 females, age=61.4±13.5 years Liberal group: n = 149, 70 males and 79 females, age=61.6±12.9 years	Restrictive group (intervention): RBC transfusion (1 unit) if Hb <7 g/dL Liberal group: RBC transfusion (1 unit) if Hb <9 g/dL HB levels assessed after IC admission, twice a day during ICU stay and after evry transfusion. Transfusion: leukodepleted RBC units	Dr. Park disclosed government work. The remaining authors have disclosed that they do not have any potential conflicts of interest. Identified from the update.
Hébert, 1995, Canada	Experimental: Randomised controlled trial	69 normovolaemic critically ill participants admitted to a tertiary level intensive care units, Hb <9.0 g/dL, randomised within 72 hours of admission (clinical specialty subgroup (Carson, 2016): critical care)	Restrictive group (intervention): transfusion if 7.0<Hb<7.5 g/dL, maintained at 7.0-9.0 g/dL Liberal group (control): transfusion if 10.0<Hb<10.5 g/dL, maintained at 10.0-12.0 g/dL	Supported by the Canadian Red Cross Society and the Physicians' Services Incorporated Foundation (charitable foundation).

		Restrictive group: n=33, 14 males and 19 females, age=58±15 years Liberal group: n=36, 19 males and 17 females, age=59±21 years	Transfusion: allogeneic RBC transfusions	Identified from the systematic review of Carson et al., 2016.
Hébert, 1999, Canada	Experimental: Randomised controlled trial	838 critically ill participants with euvolaemia after initial treatment admitted to ICU, Hb <9.0 g/dL, randomised within 72 hours of admission (clinical specialty subgroup (Carson, 2016): critical care) Restrictive group: n=418, 269 males and 149 females, age=57.1±18.1 years Liberal group: n=420, 255 males and 165 females, age=58.1±18.3 years	Restrictive group (intervention): transfusion if Hb <7.0 g/dL, and then maintained at 7.0-9.0 g/dL Liberal group (control): transfusion if Hb <10.0 g/dL, and then maintained at 10.0-12.0 g/dL Transfusion: RBC transfusions	Supported by federal agency. Unrestricted grant from industry (Bayer). One author received government grant. Identified from the systematic review of Carson et al., 2016.
Holst, 2014, Denmark	Randomised controlled trial	998 participants in Denmark, Sweden, Norway and Finland with septic shock in the ICU and haemoglobin concentration less than 9 g/dL (clinical specialty subgroup (Carson, 2016): critical care) Restrictive group: n=502, 272 males and 230 females, median age (IQR)=67 (57-73) yrs Liberal group: n=496, 259 males and 237 females, median	Restrictive group (intervention): transfusion if Hb conc ≤7.0 g/dL Liberal group (control): transfusion if Hb ≤9.0 g/dL Haemoglobin concentrations were reassessed within 3 hours after termination of the transfusion or before the initiation of another transfusion. Transfusion: single units of cross-matched, prestorage leukoreduced red cells	Research funded by hospitals, medical societies and foundations. Two authors received grant support from private industry. Identified from the systematic review of Carson et al., 2016. Two articles (one subgroup analysis and one follow-up)

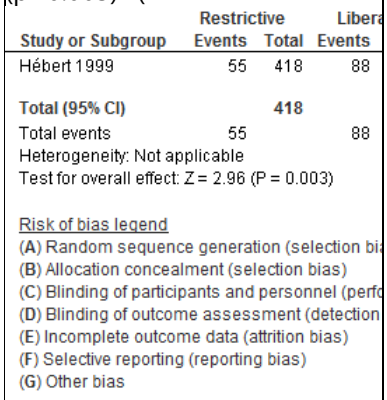
		age (IQR)=67 (58-75) yrs		identified through the updated search: Rygård 2016 (follow-up) and Rygård 2017 (subgroup analysis). Relevant additional data from Rygård 2016 was extracted and included in the synthesis of findings.
Palmieri, 2017, USA	Experimental: Randomised controlled trial	Eighteen burn centers enrolled 345 patients with 20% or more total body surface area burn. Restrictive group: n=168, 79.8% males, age=41 (IQR, 27-55) Liberal group: n=177, 78.5% males, age=41 (IQR, 30-55)	Restrictive group (intervention): transfusion if Hb <7.0 g/dL, target Hb 7.0-8.0 g/dL Liberal group (control): transfusion if Hb <10.0 g/dL, target Hb 10.0-11.0 g/dL Transfusion: RBC transfusions	This study was supported by the American Burn Association and funded by USAMRMC Award W81XWH-08-1-0760 with support from the National Center for Research Resources, National Institutes of Health, through grant UL1 RR024146, the National Center for Advancing Translational Sciences, National Institutes of Health, through grant TR 000002, and the National Center for Advancing Translational Sciences,

				National Institutes of Health through grant UL1 TR001860. Identified from update systematic review of Carson et al., 2016.
Walsh, 2013, UK	Experimental: Randomised controlled trial	ICU participants ≥55 years, Hb <9 g/dL, mechanical ventilation for ≥ 96 hours, and expected to require ≥ 24 hours of further mechanical ventilation (clinical specialty subgroup (Carson, 2016): critical care) Restrictive group: n=51, 36 males and 15 females, age=67±7 years (range: 56-80) Liberal group: n=49, 24 males and 25 females, age=68±8 years (range: 55-83)	Restrictive group (intervention): transfusion if Hb <7.0 g/dL, target Hb 7.1-9.0 g/dL Liberal group (control): transfusion if Hb <9.0 g/dL, target Hb 9.1-11.0 g/dL Transfusion: RBC transfusions	Research supported by government agencies with no influence on design or conduct. Several authors received individual government grants and/or consult for industry. Identified from the systematic review of Carson et al., 2016.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcomes				
30-day mortality	Restrictive vs liberal transfusion threshold	Not statistically significant: 366/1323 vs 380/1327 RR: 0.97, 95%CI [0.82;1.15] (p=0.75)** (Figure 1)	6, 1323 vs 1327	Bergamin 2017; Holst 2014; Hébert, 1995; Hébert ,1999; Palmieri, 2017; Walsh, 2013
30-day mortality (subgroup:		Statistically significant 18/207 vs 35/217 § RR: 0.54, 95%CI [0.32;0.92]	1, 207 vs 217	Hébert, 1999

APACHE II score ≤20)		(p=0.02)** *In favour of restrictive transfusion threshold*		
30-day mortality (subgroup: <55 years)		Statistically significant 10/173 vs 21/161 § RR: 0.44, 95%CI [0.22;0.91] (p=0.03)** *In favour of restrictive transfusion threshold*	1, 173 vs 161	Hébert, 1999
30-day mortality (subgroup: primary or secondary diagnosis of cardiac disease)		Not statistically significant 31/151 vs 40/175 § RR: 0.90, 95%CI [0.59;1.36] (p=0.61)**	1, 151 vs 175	Hébert, 1999
30-day mortality (subgroup: severe infections and septic shock)		Not statistically significant 26/114 vs 31/104 § RR: 0.77, 95%CI [0.49;1.20] (p=0.24)**	1, 114 vs 104	Hébert, 1999
Hospital mortality		Not statistically significant 263/971 vs 296/965 RR: 0.88, 95%CI [0.76;1.02] (p=0.02)** (Figure 2)	3, 971 vs 965	Holst 2014; Hébert 1999; Walsh, 2013
Participants exposed to blood transfusion		Statistically significant 726/1155 vs 1085/1150 RR: 0.68, 95%CI [0.63;0.72] (p<0.00001)** (Figure 3) *In favour of restrictive transfusion threshold*	5, 1155 vs 1150	Bergamin 2017; Holst 2014; Hébert, 1995; Hébert 1999; Walsh, 2013
Units of blood transfused		Statistically significant 2.6±4.1 vs 5.6±5.3 MD: -3.00, 95%CI [-3.64;-2.36] (p<0.00001)* (Figure 4) *In favour of restrictive transfusion threshold*	1, 418 vs 420	Hébert 1999
Number of RBC transfusions		Statistically significant 7 (IQR: 2-19) vs 15 (IQR: 7-31) Median difference: -8 (p<0.001)* *In favour of restrictive transfusion threshold*	1, 168 vs 171	Palmieri 2017
Secondary outcomes				
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	Statistically significant MD: -1.66, 95%CI [-2.15;-1.16] (p<0.00001)** (Figure 5)	3, 971 vs 965	Holst 2014; Hébert 1999; Walsh, 2013
Cardiac events		Statistically significant 55/418 vs 88/420 § RR: 0.63, 95%CI [0.46;0.85]	1, 418 vs 420	Hébert 1999

		(p=0.003)* ( Figure 6) *In favour of restrictive transfusion threshold*		
Myocardial infarction		Not statistically significant: 49/1057 vs 42/1058 § RR: 1.01, 95%CI [0.38;2.72] (p=0.98)* (Figure 7)	3, 1057 vs 1058	Bergamin 2017; Holst 2014; Hébert 1999
Congestive heart failure		Statistically significant 22/906 vs 45/909 § RR: 0.49, 95%CI [0.30;0.80] (p=0.005)* (**Fout! Verwijzingsbron niet gevonden.**) *In favour of restrictive transfusion threshold*	2, 906 vs 909	Holst 2014; Hébert 1999
Sepsis/bacteraemia		Not statistically significant: 30/418 vs 40/420 § RR: 0.75, 95%CI [0.48;1.19] ¥ (p=0.22)* (Figure 8)	1, 418 vs 420	Hébert 1999
Pneumonia or wound infection		Not statistically significant: 42/418 vs 50/420 § RR: 0.84, 95%CI [0.57;1.24] ¥ (p=0.39)* (Figure 0)		
Pneumonia		Not statistically significant: 136/586 vs 135/597 § RR: 1.03, 95%CI [0.84;1.27] ¥ (p=0.78)* (Figure 911)	2, 586 vs 597	Hébert 1999, Palmieri 2017
Blood stream infections		Not statistically significant: 40/168 vs 42/177 § RR: 1.00, 95%CI [0.69;1.46] ¥ (p=0.99)* (Figure 912)	1, 168 vs 177	Palmieri 2017
Wound infections		Not statistically significant: 20/168 vs 21/177 § RR: 1.00, 95%CI [0.56;1.78] ¥ (p=0.99)* (Figure 913)	1, 168 vs 177	Palmieri 2017
Urinary tract infections		Not statistically significant: 24/168 vs 24/177 § RR: 1.05, 95%CI [0.62;1.78] ¥ (p=0.85)* (Figure 914)	1, 168 vs 177	Palmieri 2017

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference
* Calculations (p-value) done by the reviewer(s) using Review Manager software
** Calculations (RR or MD, 95% CI and p-value) done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events

Forest plots

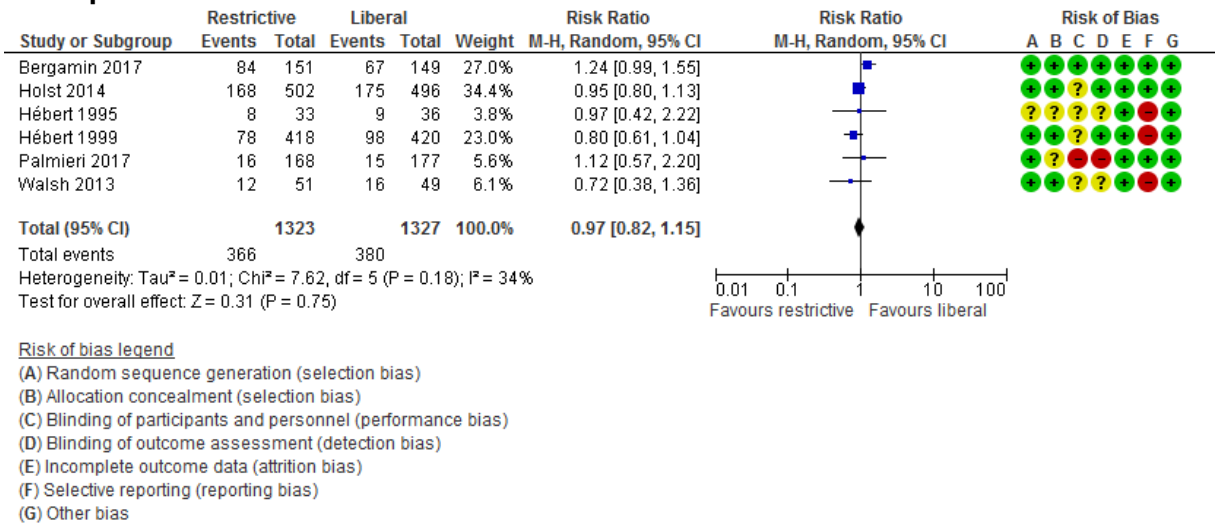


Figure 1: Forest plot of outcome: 30-day mortality.

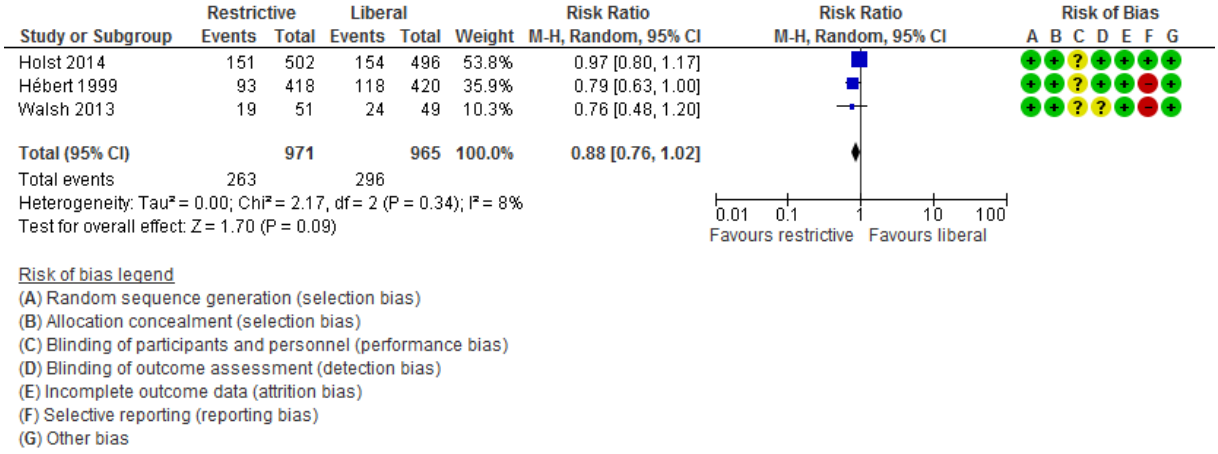


Figure 2: Forest plot of outcome: Hospital mortality.

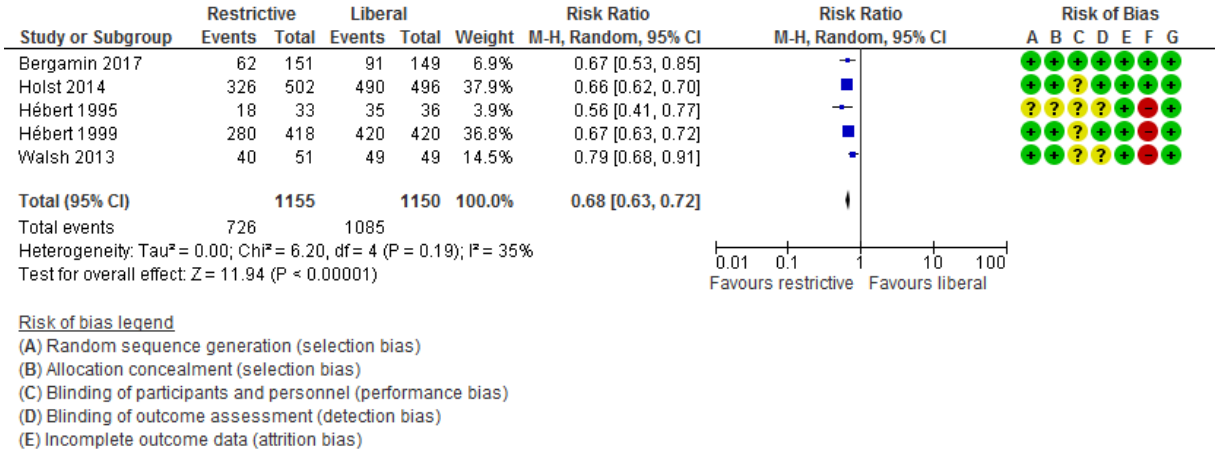
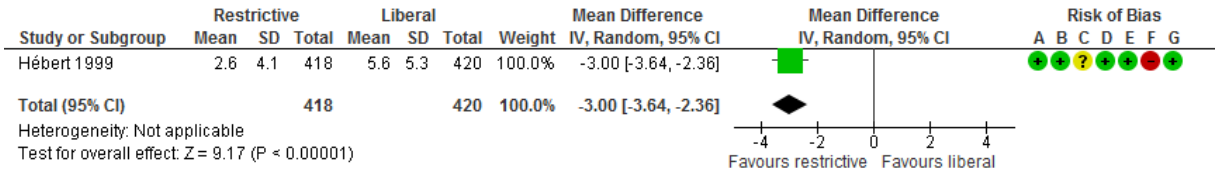
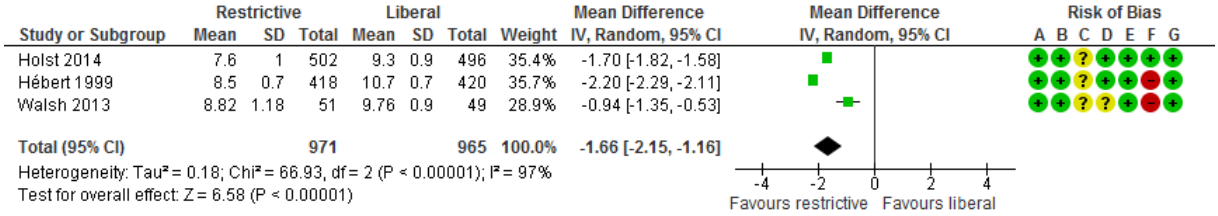


Figure 3: Forest plot of outcome: Participants exposed to blood transfusion.



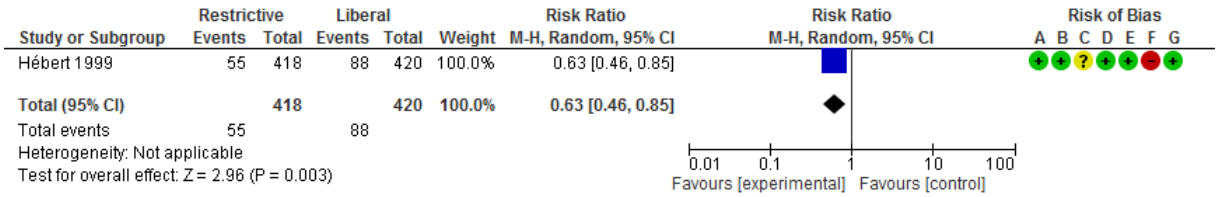
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4: Forest plot of outcome: Units of blood transfused.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 5: Forest plot of outcome: Haemoglobin concentration.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 6: Forest plot of outcome: Cardiac events.

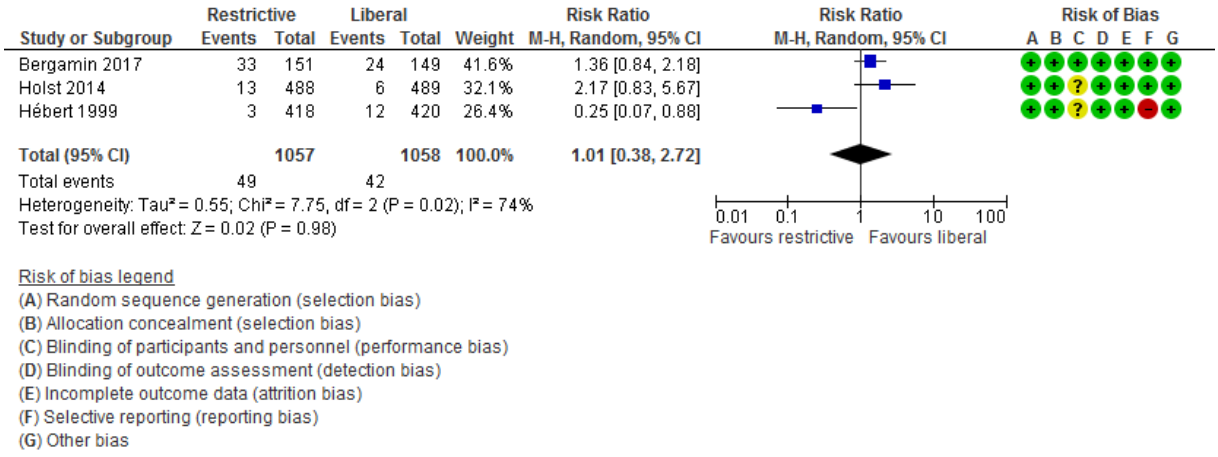


Figure 7: Forest plot of outcome: Myocardial infarction.

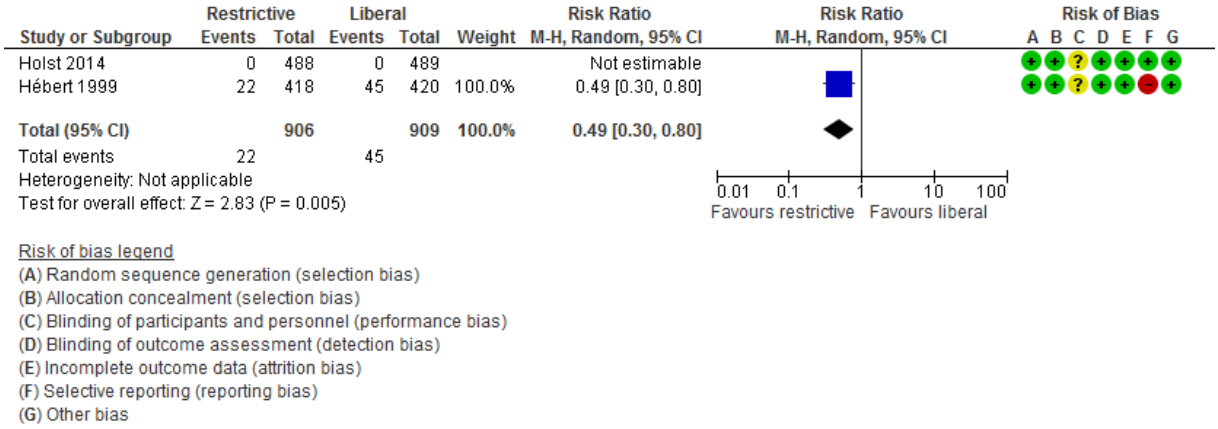


Figure 8: Forest plot of outcome: Congestive heart failure.

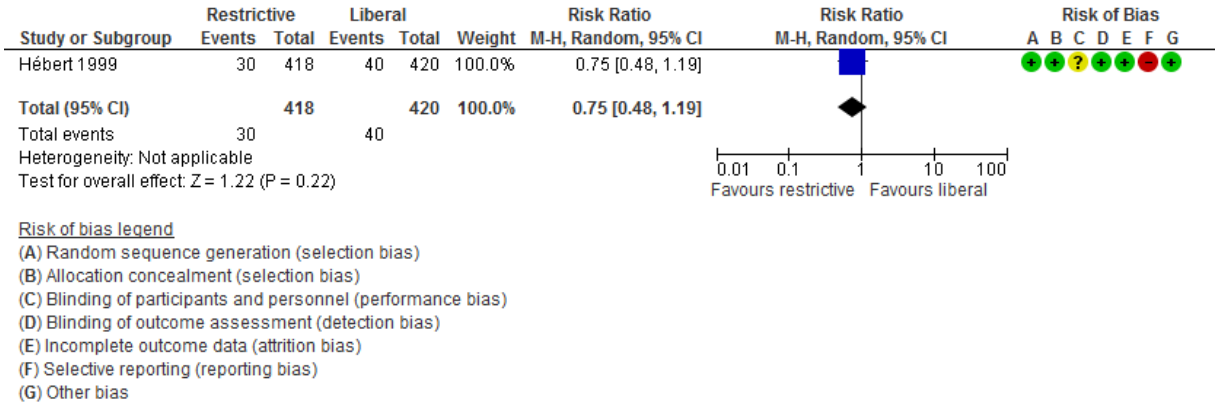


Figure 8: Forest plot of outcome: Sepsis/bacteraemia.

Figure 10: Forest plot of outcome: Pneumonia or wound infection.

Figure 91: Forest plot of outcome: Pneumonia.

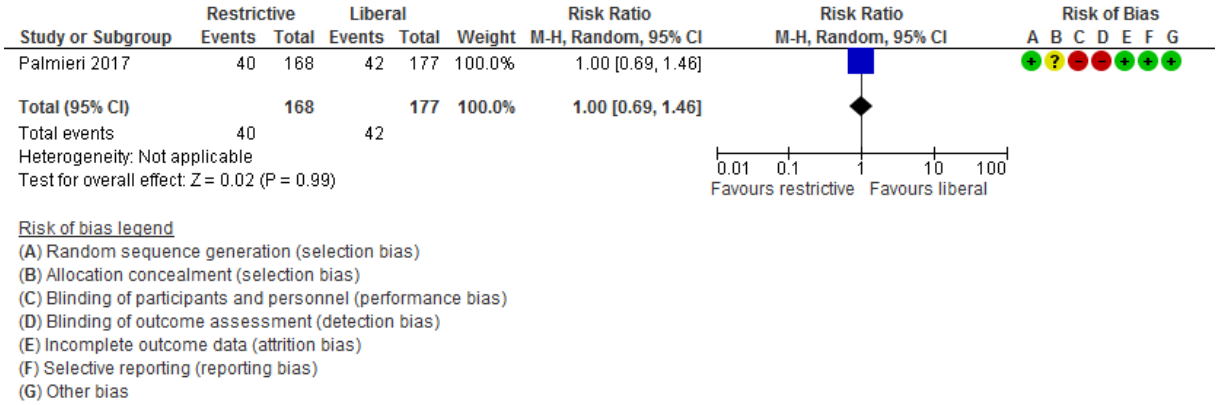


Figure 102: Forest plot of outcome: Blood stream infections.

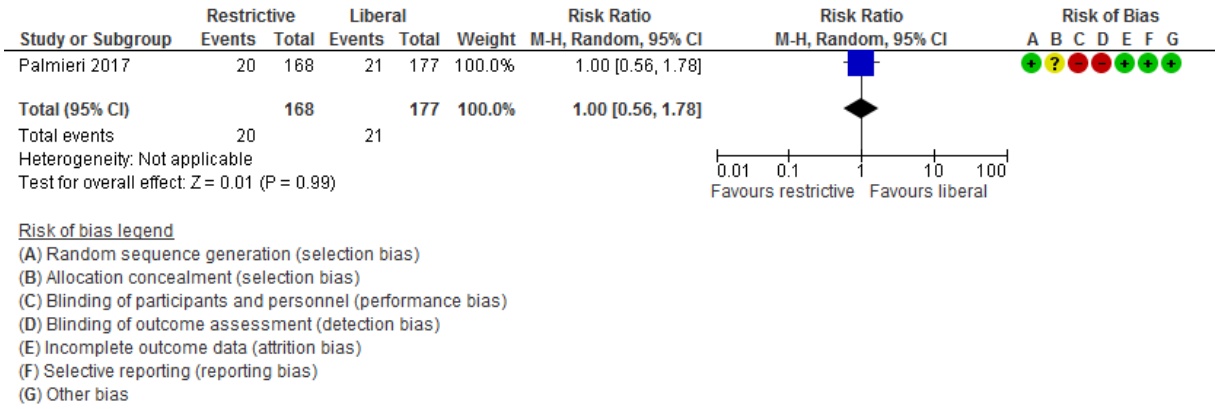


Figure 113: Forest plot of outcome: Wound infections.

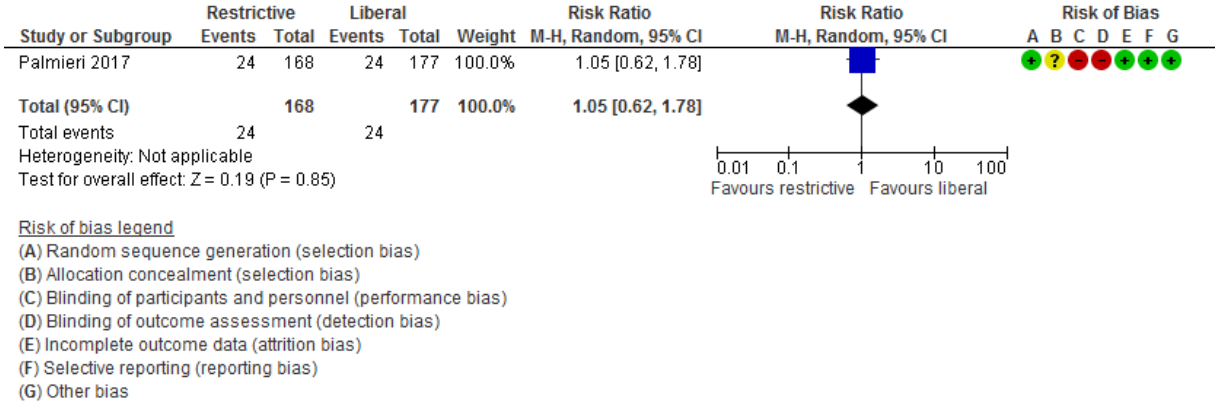


Figure 124: Forest plot of outcome: Urinary tract infections.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Bergamin, 2017	Randomization: no, an internet-based system was used Allocation concealment: no internet-based system concealed assignments	Personnel and participants: no, physicians and nurses of the ICU were aware, patients and investigators were blinded Outcome assessment: no, 2 blinded investigators assessed outcomes	No, no exclusions after randomization or loss to follow-up	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT01648946)	No
Hébert, 1995	Randomization: Unclear, assigned to 1 of 2 groups by consecutive allocation from a random listing stratified by centre and disease severity. Allocation concealment: Unclear, no information.	Participants and personnel: Unclear, blinding was not feasible but unlikely to be important. Outcome assessors: Unclear, not specified.	No	Yes No pre-registration of study protocol	No
Hébert, 1999	Randomization: No, computer generated randomization. Allocation concealment: No, sealed opaque envelopes prepared by data co-ordinating centre, opened sequentially in ICU to determine participants assignment	Participants and personnel: Unclear, unfeasible to blind personnel. Patients were in ICU. Outcome assessors: No for mortality (primary outcome), Yes for cardiac events, myocardial infarction, heart failure, sepsis,	No	Yes No pre-registration of study protocol	No definitions provided for cardiac events, myocardial infarction, heart failure, sepsis, pneumonia and wound infection

		pneumonia and wound infection			
Holst, 2014	Randomization: No, a centralised computer generated the assignment sequence. Allocation concealment: No, use of a centralised computer ensured allocation concealment.	Participants and personnel: Unclear, clinicians were not blinded. Outcome assessors: No, the investigators assessing mortality (the DSMB) and the trial statistician were blinded.	main study (Holst 2014): No, near complete follow-up. follow-up study (Rygård 2016 identified in search update): Unclear, considerable loss to follow-up for health survey questionnaire. Responders are older and suffered more often had a pulmonary source of sepsis. Among responders, baseline characteristics were similar in the two intervention groups.	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT01485315)	No
Palmieri, 2017	Randomization: adaptive random allocation procedure was used + "biased coin" procedure. Allocation concealment: Unclear, no information.	Participants and personnel: yes Outcome assessors: yes Investigators were informed of treatment group by calling the randomization center, which used the computer-generated randomization	No No lost to follow-up in both groups, Discontinued intervention: n=10 in restrictive group, n=19 in liberal group. Intention-to-treat analysis	No Study protocol registered @ ClinicalTrials.Gov (NCT01079247)	No

		scheme described above to provide treatment assignments.	was performed.		
Walsh, 2013	Randomization: No, minimisation by centre and the presence of ischaemic heart disease, including a random element, was used Allocation concealment: No, telephone randomisation.	Participants and personnel: Unclear, clinicians not blinded. Most surviving participants were unaware of allocation. Outcome assessors: Unclear, researchers administering questionnaires were blinded, but assessment of clinical outcomes was not documented to have been done blindly.	No, good follow-up.	Yes No pre-registration of study protocol	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **Bergamin 2017** Bergamin FS, Almeida JP, Landoni G, Galas FRBG, Fukushima JT, Fominskiy E, Park CHL, Osawa EA, Diz MPE, Oliveira GQ, Franco RA, Nakamura RE, Almeida EM, Abdala E, Freire MP, Filho RK, Auler JOC Jr, Hajjar LA. *Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial.* Crit Care Med. 2017, 45(5):766-773. Identified in search update. **Hébert 1995** Hébert PC, Wells G, Marshall J, Martin C, Tweeddale M, Pagliarello G, et al. *Transfusion requirements in critical care. A pilot study.* Canadian Critical Care Trials Group [published erratum appears in JAMA 1995, 274(12): 944]. JAMA 1995, 273(18):1439–1444. **Hébert, 1999** Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, et al. *A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture.* Transfusion 1998, 38(6):522–529. *Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. *A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group*. N Engl J Med 1999, 340(6):409–417.

	McIntyre L, Hebert PC, Wells G, Fergusson D, Marshall J, Yetisir E, et al. Canadian Critical Care Trials Group. *Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients?* J Trauma 2004, 57(3):563–568. **Holst 2014** *Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. TRISS Trial Group. Scandinavian Critical Care Trials Group. *Lower versus higher hemoglobin threshold for transfusion in septic shock*. N Engl J Med 2014, 371(15):1381-91. Rygård SL, Holst LB, Wetterslev J, Winkel P, Johansson PI, Wernerman J, et al. TRISS Trial Group. Scandinavian Critical Care Trials Group. *Long-term outcomes in patients with septic shock transfused at a lower versus a higher haemoglobin threshold: the TRISS randomised, multicentre clinical trial*. Intensive Care Med 2016, 42(11):1685-1694. Identified in search update. Rygård SL, Holst LB, Wetterslev J, Johansson PI, Perner A. TRISS trial group. Scandinavian Critical Care Trials Group. *Higher vs. lower haemoglobin threshold for transfusion in septic shock: subgroup analyses of the TRISS trial*. Acta Anaesthesiol Scand 2017, 61(2):166-175. Identified in search update. **Palmieri, 2017** Palmieri TL, Holmes, JH, Arnoldo B, Peck, M, Potenza B, Cochran A, King BT, Dominic W, Cartotoo R, Bhavsar D, Kemalyan N, Tredget E, Stapelberg F, Mozingo D, Friedman B, Greenhalgh DG, Taylor SL, Pollock BH. *Transfusion Requirement in Burn Care Evaluation (TRIBE). A multicentre randomized prospective trial of blood transfusion in major burn injury*. Annals of Surgery 2017, 266(4):595-602. **Walsh, 2013** Walsh TS, Boyd JA, Watson D, Hope D, Lewis S, Krishan A, et al. *Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial*. Crit Care Med 2013, 41(10): 2354–2363. **Systematic reviews** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion*. Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease*. In peer-review [February 2018]. *Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 5: RBC transfusion triggers in adult orthopaedic/non-cardiac surgery patients

Overview evidence table GRADE software (PICO 5)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
30-day mortality (overall)												
7	randomised trials	not serious	not serious	not serious	serious [a]	none	79/1467 (5.4%)	72/1463 (4.9%)	**RR 1.18** (0.75 to 1.85)	**9 more per 1.000** (from 12 fewer to 42 more)	⊕⊕⊕◯ MODERATE	CRITICAL
30-day mortality (subgroup: orthopaedic surgery)												
6	randomised trials	not serious	not serious	not serious	serious [a]	none	75/1417 (5.3%)	68/1414 (4.8%)	**RR 1.27** (0.72 to 2.25)	**13 more per 1.000** (from 13 fewer to 60 more)	⊕⊕⊕◯ MODERATE	CRITICAL
30-day mortality (subgroup: vascular surgery)												
1	randomised trials	serious [b]	not serious	serious [c]	serious [a]	none	4/50 (8.0%)	4/49 (8.2%)	**RR 0.98** (0.26 to 3.70)	**2 fewer per 1.000** (from 60 fewer to 220 more)	⊕◯◯◯ VERY LOW	CRITICAL
Hospital mortality (overall)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	randomised trials	serious [d]	not serious	not serious	serious [a]	none	14/1369 (1.0%)	25/1272 (2.0%)	**RR 0.55** (0.25 to 1.25)	**9 fewer per 1.000** (from 5 more to 15 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospital mortality (subgroup: orthopaedic surgery)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	14/1344 (1.0%)	23/1245 (1.8%)	**RR 0.45** (0.09 to 2.28)	**10 fewer per 1.000** (from 17 fewer to 24 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital mortality (subgroup: abdominal surgery)												
1	randomised trials	serious [d]	not serious	serious [e]	serious [f]	none	0/25 (0.0%)	2/27 (7.4%)	**RR 0.22** (0.01 to 4.28)	**58 fewer per 1.000** (from 73 fewer to 243 more)	⨁◯◯◯ VERY LOW	CRITICAL
90-day mortality (orthopaedic surgery)												
2	randomised trials	not serious	not serious	serious [g]	serious [a]	none	51/244 (20.9%)	40/240 (16.7%)	**RR 1.25** (0.87 to 1.81)	**42 more per 1.000** (from 22 fewer to 135 more)	⨁⨁◯◯ LOW	CRITICAL
Patients exposed to RBC transfusion (overall)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
12	randomised trials	not serious	not serious [h]	not serious	not serious	none	809/2026 (39.9%)	1659/2032 (81.6%)	**RR 0.50** (0.38 to 0.67)	**408 fewer per 1.000** (from 269 fewer to 506 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Patients exposed to RBC transfusion (subgroup: orthopaedic surgery)												
10	randomised trials	not serious	not serious [h]	not serious	not serious	none	760/1951 (39.0%)	1597/1956 (81.6%)	**RR 0.50** (0.38 to 0.67)	**408 fewer per 1.000** (from 269 fewer to 506 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Patients exposed to RBC transfusion (subgroup: vascular surgery)												
1	randomised trials	not serious	not serious	serious [c]	serious [f]	none	40/50 (80.0%)	43/49 (87.8%)	**RR 0.91** (0.77 to 1.08)	**79 fewer per 1.000** (from 70 more to 202 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Patients exposed to RBC transfusion (subgroup: abdominal surgery)												
1	randomised trials	not serious	not serious	serious [e]	serious [f]	none	9/25 (36.0%)	19/27 (70.4%)	**RR 0.51** (0.29 to 0.91)	**345 fewer per 1.000** (from 63 fewer to 500 fewer)	⨁⨁◯◯ LOW	IMPORTANT
RBC units transfused (overall)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious [i]	not serious	serious [j]	not serious	none	349	353	-	MD **0.23 units lower** (0.85 lower to 0.39 higher)	⊕⊕◯◯ LOW	IMPORTANT
RBC units transfused (subgroup: orthopaedic surgery)												
1	randomised trials	serious [i]	not serious	serious [k]	not serious	none	299	304	-	MD **0.08 units lower** (0.32 lower to 0.16 higher)	⊕⊕◯◯ LOW	IMPORTANT
RBC units transfused (subgroup: vascular surgery)												
1	randomised trials	serious [i]	not serious	serious [c]	serious [a]	none	50	49	-	MD **0.9 units lower** (2.2 lower to 0.4 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
RBC units transfused (subgroup: abdominal surgery)												
1	randomised trials	serious [i]	not serious	serious [e]	serious [l]	none	25	27	-	median **1 unit lower** (0 to 0)	⊕◯◯◯ VERY LOW	IMPORTANT
Haemoglobin concentration (overall)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
6	randomised trials	not serious	not serious	not serious	not serious	none	1532	1534	-	MD **0.99 lower** (1.53 lower to 0.45 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Haemoglobin concentration (subgroup: orthopaedic surgery)												
4	randomised trials	not serious	not serious	not serious	not serious	none	1457	1458	-	MD **0.9 units lower** (1.6 lower to 0.2 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Haemoglobin concentration (subgroup: vascular/abdominal surgery)												
2	randomised trials	not serious	not serious	not serious	serious [l]	none	75	76	-	MD **1.2 units lower** (1.57 lower to 0.83 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Cardiac events (overall)												
4	randomised trials	not serious	not serious	not serious	not serious	none	116/1420 (8.2%)	87/1425 (6.1%)	**RR 1.32** (1.01 to 1.72)	**20 more per 1.000** (from 1 more to 44 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cardiac events (subgroup: orthopaedic surgery)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
3	randomised trials	not serious	not serious	not serious	not serious	none	108/1370 (7.9%)	79/1376 (5.7%)	**RR 1.36** (1.03 to 1.80)	**21 more per 1.000** (from 2 more to 46 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cardiac events (subgroup: vascular surgery)												
1	randomised trials	serious [d]	not serious	not serious	serious [a]	none	8/50 (16.0%)	8/49 (16.3%)	**RR 0.98** (0.40 to 2.40)	**3 fewer per 1.000** (from 98 fewer to 229 more)	⊕⊕◯◯ LOW	CRITICAL
Myocardial infarction (overall)												
6	randomised trials	not serious	not serious	not serious	serious [a]	none	41/1384 (3.0%)	27/1382 (2.0%)	**RR 1.50** (0.93 to 2.42)	**10 more per 1.000** (from 1 fewer to 28 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Myocardial infarction (subgroup: orthopaedic surgery)												
5	randomised trials	not serious	not serious	not serious	serious [a]	none	40/1334 (3.0%)	25/1333 (1.9%)	**RR 1.58** (0.97 to 2.56)	**11 more per 1.000** (from 1 fewer to 29 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Myocardial infarction (subgroup: vascular surgery)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [d]	not serious	not serious	serious [f]	none	1/50 (2.0%)	2/49 (4.1%)	**RR 0.49** (0.05 to 5.23)	**21 fewer per 1.000** (from 39 fewer to 173 more)	⊕⊕◯◯ LOW	CRITICAL
Congestive heart failure (subgroup: orthopaedic surgery)												
4	randomised trials	not serious	not serious	not serious	serious [a]	none	39/1263 (3.1%)	30/1263 (2.4%)	**RR 1.28** (0.80 to 2.05)	**7 more per 1.000** (from 5 fewer to 25 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
CVA-stroke (subgroup: orthopaedic surgery)												
5	randomised trials	serious [d]	not serious	not serious	serious [a]	none	5/1305 (0.4%)	13/1301 (1.0%)	**RR 0.43** (0.16 to 1.13)	**6 fewer per 1.000** (from 1 more to 8 fewer)	⊕⊕◯◯ LOW	CRITICAL
Sepsis-bacteraemia (subgroup: orthopaedic surgery)												
2	randomised trials	serious [d]	not serious	not serious	serious [a]	none	2/399 (0.5%)	2/404 (0.5%)	**RR 0.96** (0.14 to 6.55)	**0 fewer per 1.000** (from 4 fewer to 27 more)	⊕⊕◯◯ LOW	IMPORTANT
Pneumonia (subgroup: orthopaedic surgery)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
8	randomised trials	not serious	not serious	not serious	serious [a]	none	84/1778 (4.7%)	105/1778 (5.9%)	**RR 0.83** (0.63 to 1.09)	**10 fewer per 1.000** (from 5 more to 22 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pneumonia or wound infection (subgroup: orthopaedic surgery)												
4	randomised trials	not serious	not serious	not serious	serious [a]	none	182/1512 (12.0%)	209/1511 (13.8%)	**RR 0.76** (0.50 to 1.16)	**33 fewer per 1.000** (from 22 more to 69 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Thromboembolism (subgroup: orthopaedic surgery)												
6	randomised trials	not serious	not serious	not serious	serious [a]	none	12/1604 (0.7%)	17/1605 (1.1%)	**RR 0.71** (0.34 to 1.47)	**3 fewer per 1.000** (from 5 more to 7 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Renal failure (subgroup: orthopaedic surgery)												
2	randomised trials	serious [m]	not serious	not serious	serious [a]	none	2/194 (1.0%)	3/192 (1.6%)	**RR 0.73** (0.14 to 3.84)	**4 fewer per 1.000** (from 13 fewer to 44 more)	⊕⊕◯◯ LOW	CRITICAL
Mental confusion (subgroup: orthopaedic surgery)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
6	randomised trials	serious [m]	not serious	not serious	serious [a]	none	61/668 (9.1%)	66/676 (9.8%)	**RR 0.92** (0.65 to 1.30)	**8 fewer per 1.000** (from 29 more to 34 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Inability to walk or death at 30 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	481/1000 (48.1%)	459/995 (46.1%)	**RR 1.04** (0.95 to 1.14)	**18 more per 1.000** (from 23 fewer to 65 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Inability to walk or death at 60 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	347/1001 (34.7%)	351/998 (35.2%)	**RR 0.99** (0.87 to 1.11)	**4 fewer per 1.000** (from 39 more to 46 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower extremity physical activities of daily living at 30 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	507	472	-	MD **0.2 points higher** (0.26 lower to 0.66 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Lower extremity physical activities of daily living at 60 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	553	523	-	MD **0 points** (0.51 lower to 0.51 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Instrumental activities of daily living at 30 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	450	437	-	MD **0 points** (0.06 lower to 0.06 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Instrumental activities of daily living at 60 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	411	389	-	MD **0 points** (0.12 lower to 0.12 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Energy/fatigue at 30 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	459	456	-	MD **0.1 lower** (1.09 lower to 0.89 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8-9 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Energy/fatigue at 60 days (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	525	544	-	MD **0.5 points higher** (0.38 lower to 1.38 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Timed up and go test (subgroup: orthopaedic surgery)												
1	randomised trials	not serious	not serious	not serious	serious [l]	none	25	28	-	MD **6 seconds higher** (0 to 0)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Large variability in results; b. Selection bias (randomization + allocation concealment unclear), performance bias (lack of blinding unclear), reporting bias (no pre-registration study protocol); c. Lack of generalizibility: Single centre study conducted in the USA; d. Detection bias and reporting bias; e. Lack of generalizibility: Single centre study conducted in Greece; f. Low number of events, limited sample size and/or large variability in results; g. Lack of generalizibliity: 2 small single centre studies form UK and Denmark; h. Decision not to downgrade by reviewer(s) although point estimates vary, CIs show minimal or no overlap, tests for heterogeneity show a low p-value and I2>75%. This large inconsistency or variability is, however, not considered important as the direction of effect is the same for all studies which is most relevant for this outcome; i. Detection bias unclear, no pre-registration of study protocol; j. Lack of generalizibility: 1 (old) small study from USA + 1 study conducted in The Netherlands; k. Lack of generalizibliity: one study conducted in The Netherlands; l. Low number of events and/or limited sample size; m. Detection bias and selection bias.

Detailed evidence summary (PICO 5)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In elderly high risk (cardiovascular) patients undergoing orthopaedic or non-cardiac surgery (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. <u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6 **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 **Embase** (via Embase.com interface) using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 **Transfusion evidence library** (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: elderly high risk (cardiovascular) patients undergoing a) orthopaedic surgery (e.g. knee or hip surgery) or b) non-cardiac surgery (e.g. vascular surgery and abdominal surgery). **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction,

	congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** Systematic reviews (+ meta-analyses) of experimental studies (RCT's). If systematic reviews (published within 5 years of the search date) are not available, we will search for individual experimental studies (RCT's). To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes**.**

Characteristics of included studies
Studies also labeled according to age of the population:

- Elderly: all participants ≥65 years old
- Older: mean age of participants ≥64 years old
- Younger: participants of all ages

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Bush, 1997, USA	Randomised controlled trial	99 participants undergoing elective aortic or infrainguinal arterial reconstruction (clinical specialty subgroup (Carson, 2016): vascular surgery) Restrictive group: n=50, 32 males and 18 females, age=66±10 years Liberal group: n=49, 41 males and 8 females, age=64±11 years Age of population: older	Restrictive group (intervention): transfusion if Hb <9.0 g/dL Liberal group (control): Hb maintained ≥10.0 g/dL Transfusion: Predonated autologous blood (restrictive group: n=1, liberal group: n=3) if available or allogeneic blood	No information available on study funding or financial COI. Identified from the systematic review of Carson et al., 2016.
Carson, 1998, USA	Randomised controlled trial	84 hip fracture participants (in USA and Scotland) undergoing surgical repair with postoperative Hb<10.0 g/dL	Restrictive group (intervention): transfusion permitted if symptoms of anemia or Hb<8g/dL;	No information available on study funding or financial COI.

		(clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=42, 11 males and 31 females, age=83.3±10.8 years Liberal group: n=42, 9 males and 33 females, age=81.3±8.1 years Age of population: older	1 unit at a time until symptoms disappeared or Hb increased >8 g/dL Liberal group (control): immediately transfuse 1 unit after randomisation (Hb<10 g/dL) and transfuse enough blood to maintain Hb>10 g/dL Transfusion: units of packed RBC (allogeneic)	Identified from the systematic review of Carson et al., 2016.
Carson, 2011, USA	Randomised controlled trial	2016 participants (>50 years, in USA and Canada) undergoing surgical repair of a hip fracture with Hb<10.0 g/dL who had clinical evidence of cardiovascular disease or cardiovascular risk factors (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=1009, 239 males and 770 females, age=81.5±9.0 years Liberal group: n=1007, 250 males and 757 females, age=81.8±8.8 years Age of population: older	Restrictive group (intervention): transfusion permitted if symptoms of anaemia or Hb<8g/dL; 1 unit at a time until symptoms disappeared or Hb increased >8 g/dL Liberal group (control): immediately transfuse 1 unit after randomisation (Hb<10 g/dL) and transfuse enough blood to maintain Hb>10 g/dL Transfusion: units of packed RBC	Study partly funded by National Heart, Lung and Blood Institute. Research institute does receive grant support from industry. Several authors also work with industry. Identified from the systematic review of Carson et al., 2016.
Fan, 2014, China	Randomised controlled trial	186 participants (>65 years) undergoing elective unilateral total hip replacement (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=94, 30 males and 64 females, age=73±7 years	Restrictive group (intervention): transfusion if symptoms of anemia or Hb<8g/dL Liberal group (control): transfuse enough blood to maintain Hb>10 g/dL	Research funded by government grants. No conflicts of interest stated. Identified from the systematic review of Carson et al., 2016.

		Liberal group: n=92, 33 males and 59 females, age=75±6 years Age of population: elderly	Transfusion: units of blood	
Foss, 2009, Denmark	Randomised controlled trial	120 hip fracture participants (>65 years) (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=60, 14 males and 46 females, age=81±7.3 years Liberal group: n=60, 114 males and 46 females, age=81±6.8 years Age of population: elderly	Restrictive group (intervention): transfusion with RBC if Hb conc <8.0 g/dL (7.2 g/dL<Hb<8 g/dL: 1 unit of RBC; 5.6 g/dL<Hb≤7.2 g/dL: 2 units of RBC; Hb<5.6 g/dL: 3 units of RBC; all transfusions followed by control of Hb) Liberal group (control): transfusion with RBC if Hb <10.0 g/dL (8.8 g/dL<Hb<10 g/dL: 1 unit of RBC; 7.2 g/dL<Hb≤8.8 g/dL: 2 units of RBC; Hb<7.2 g/dL: 3 units of RBC, all transfusions followed by control of Hb) Transfusion: RBC unit	Research support by private foundation (IMK Almene Fond). No conflict of interest declared. Identified from the systematic review of Carson et al., 2016.
Gregersen, 2015, Denmark	Randomised controlled trial	284 participants (≥65 years) undergoing hip fracture surgery with postoperative 9.7 g/dL<Hb 11.3 g/dL (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=144, 36 males and 108 females, age=86±6.8 years Liberal group: n=140, 34 males and 106 females, age=88±6.9 years Age of population: elderly	Restrictive group (intervention): transfusion if Hb<9.7 g/dL until target achieved with max 2 units per day Liberal group (control): transfusion if Hb<11.3 g/dL until target achieved with max 2 units per day Transfusion: 1 RBC unit	Research supported by university and foundation established at university. No conflict of interest declared. Identified from the systematic review of Carson et al., 2016.

Grover, 2006, UK	Randomised controlled trial	260 participants undergoing elective lower limb joint replacement surgery (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=109, 48 males and 61 females, age=70.7±7.1 years Liberal group: n=109, 55 males and 54 females, age 71.5±7.6 years Age of population: older	Restrictive group (intervention): transfusion if Hb<8.0 g/dL, Hb conc maintained at 8.0-9.5 g/dL Liberal group (control): transfusion if Hb<10.0 g/dL, Hb conc maintained at 10.0-12.0 g/dL Transfusion: RBC unit	Study funded by government grant (NHS). Identified from the systematic review of Carson et al., 2016.
Lotke, 1999, USA	Randomised controlled trial	152 participants undergoing primary total knee arthroplasty (TKA) (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=62, 20 males and 42 females, mean age=68.7 years Liberal group: n=65, 19 males and 46 females, mean age=69.7 years Age of population: older [an additional 25 participants did not predonate blood and were not included in the systematic review]	Restrictive group (intervention): transfusion of the 2 units of autologous blood if Hb <9.0 g/dL Liberal group (control): transfusion of the 2 units of autologous blood immediately after surgery in the recovery room Transfusion: preoperatively donated autologous blood [patients who did not donate prior to surgery, excluded from systematic review data]	No information available on study funding or financial COI. Identified from the systematic review of Carson et al., 2016.
Markatou, 2012, Greece	Randomised controlled trial	52 participants scheduled for elective upper major abdominal surgery Restrictive group: n=25, 13 males and 12 females, mean age=58.2±11.7 years Liberal group:	Restrictive group (intervention): transfusion if Hb <7.7 g/dL, target Hb 7.7-9.9 g/dL Liberal group (control): transfusion if Hb <9.9 g/dL, target Hb >10 g/dL	No information available on study funding or financial COI. Identified from the systematic review of Hovaguimian and Myles, 2016.

		n=27, 16 males and 11 females, mean age=63.4±11.3 years Age of population: younger	Transfusion: RBC unit	
Nielsen, 2014, Denmark	Randomised controlled trial	66 participants (>18 years) scheduled for elective hip revision surgery (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=33, 16 males and 17 females, median age (5%-95% range)=68 (43-86) years Liberal group: n=33, 20 males and 13 females, median age (5%-95% range)=72 (53-89) years Age of population: older	Restrictive group (intervention): transfusion if Hb<7.3 g/dL with target range of 7.3-8.9 g/dL Liberal group (control): transfusion if Hb<8.9 g/dL with target >8.9 g/dL Transfusion: allogeneic RBC	Research funded by foundation from insurance company, but foundation was not involved in study design, data analysis or manuscript approval. No conflict of interest declared. Identified from the systematic review of Carson et al., 2016.
Parker, 2013, UK	Randomised controlled trial	200 participants (>60 years) with hip fracture, 8.0 g/dL<Hb<9.5 g/dL (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group: n=100, 15 males and 85 females, mean age (range)=84.2 (60-97) years Liberal group: n=100, 17 males and 83 females, mean age (range)=84.4 (60-104) years Age of population: older	Restrictive group (intervention): transfusion only if definite symptoms of anemia Liberal group (control): transfusion of at least 1 unit of blood and then maintained >10.0 g/dL Transfusion: units of blood	No external funding. No conflict of interest. Identified from the systematic review of Carson et al., 2016.
So-Osman, 2013, The Netherlands	Randomised controlled trial	603 participants in 3 hospitals undergoing elective orthopaedic surgery (clinical specialty subgroup (Carson, 2016): orthopaedic surgery) Restrictive group:	This is a post-hoc analysis of an earlier randomized controlled trial (So-Osman 2010) which is re-analyzed to create Restrictive group (intervention):	Study fully supported by grant from participating hospital. No conflicts of interest declared. Identified from the systematic

		n=299, 109 males and 190 females, age=70.2±10.3 years Liberal group: n=304, 93 males and 211 females,, age=70.7±9.6 years Age of population: older	according to new protocol hospital 1 and 2 and to the standard protocol in hospital 3 Liberal group (control): according to standard protocol in hospital 1 and 2 and to new protocol in hospital 3 Hb threshold values were based on age and comorbidities, details are provided in Appendix paper So-Osman et al. (2013) Transfusion: pre-storage leucocyte-depleted RBC units	review of Carson et al., 2016. Re-analysis of So-Osman (2010) by pooling the patients who were randomised to the most restrictive trigger to a restrictive policy group and the patients who were randomised to the most liberal transfusion policy to a liberal policy group, thereby respecting the randomised nature of the data.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcomes				
30-day mortality	Restrictive vs liberal transfusion threshold	*Overall:* Not statistically significant: 79/1467 vs 72/1463 RR: 1.18, 95%CI [0.75;1.85] ¥ (p=0.48)* (Figure 13)	7, 1467 vs 1463	Carson, 1998; Carson, 2011; Foss, 2009; Gregersen, 2015; Lotke, 1999; Parker, 2013; Bush, 1997 (vascular)
		Subgroup orthopaedic surgery: Not statistically significant: 75/1417 vs 68/1414 RR: 1.27, 95%CI [0.72;2.25] ¥ (p=0.41) (Figure 13)	6, 1417 vs 1414	Carson, 1998; Carson, 2011; Foss, 2009; Gregersen, 2015; Lotke, 1999; Parker, 2013
		Subgroup other surgery:	1, 50 vs 49	Bush, 1997

		Not statistically significant: 4/50 vs 4/49 § RR: 0.98, 95%CI [0.26;3.70] ¥ (p=0.98) (Figure 13)		(vascular)
Hospital mortality		*Overall:* Not statistically significant: 14/1369 vs 25/1272 RR: 0.55, 95%CI [0.25;1.25] ¥ (p=0.16)* (Figure 14)	4, 1369 vs 1272	
		Subgroup orthopaedic surgery: Not statistically significant: 14/1344 vs 23/1245 RR:0.45 , 95%CI [0.09;2.28] ¥ (p=0.33)* (Figure 14)	3, 1344 vs 1245	Carson, 1998; Carson, 2011; So-Osman, 2013
		Subgroup other surgery: Not statistically significant: 0/25 vs 2/27 § RR: 0.22, 95%CI [0.01;4.28] ¥ (p=0.31)* (Figure 14)	1, 25 vs 27	Markatou, 2012 (abdominal)
90-day mortality		*Orthopaedic surgery:* Not statistically significant: 51/244 vs 40/240 RR: 1.25, 95%CI [0.87;1.81] ¥ (p=0.23)* (Figure 15)	2, 244 vs 240	Gregersen, 2015; Parker, 2013
Participants exposed to blood transfusion		*Overall:* <u>Statistically significant:</u> 809/2026 vs 1659/2032 RR: 0.53, 95%CI [0.41;0.69] (p<0.00001)* (Figure 16) *In favour of restrictive transfusion threshold*	12, 2026 vs 2032	
		Subgroup orthopaedic surgery: <u>Statistically significant:</u> 760/1951 vs 1597/1956 RR: 0.50, 95%CI [0.38;0.67] (p<0.00001) (Figure 16) *In favour of restrictive transfusion threshold*	10, 1951 vs 1956	Carson, 1998; Carson, 2011; Fan, 2014;Foss, 2009; Gregersen, 2015; Grover, 2006 Lotke, 1999; Nielsen, 2014; Parker, 2013; So-Osman, 2013
		Subgroup other surgery (vascular): Not statistically significant: 40/50 vs 43/49 § RR: 0.91, 95%CI [0.77;1.08] ¥	1, 50 vs 49	Bush, 1997 (vascular);

		(p=0.30)* (Figure 16)		
		Subgroup other surgery (abdominal): <u>Statistically significant:</u> 9/25 vs 19/27 § RR: 0.51, 95%CI [0.77;1.08] ¥ (p=0.02)* (Figure 16) *In favour of restrictive transfusion threshold*	1, 25 vs 27	Markatou, 2012 (abdominal)
Units of blood transfused		*Overall:* Not statistically significant: MD: -0.23, 95%CI [-0.85;0.39] (p=0.47)* (Figure 17)	2, 349 vs 353	
		Subgroup orthopaedic surgery: Not statistically significant: 0.78±1.4 vs 0.86±1.6 MD: -0.08, 95%CI [-0.32;0.16] (p=0.51)* (Figure 17)	1, 299 vs 304	So-Osman, 2013
		Subgroup other surgery: Not statistically significant: 2.8±3.1 vs 3.7±3.5 MD: -0.90, 95%CI [-2.20;0.40] ¥ (p=0.18)** (Figure 17)	1, 50 vs 49 §	Bush, 1997 (vascular)
		Subgroup other surgery: <u>Statistically significant:</u> median [IQR]: 0 [0,2] vs 1 [0,3] (p=0.013)	1, 25 vs 27 §	Markatou, 2012 (abdominal)
Secondary outcomes				
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	*Overall:* <u>Statistically significant:</u> MD: -0.99, 95%CI [-1.53;-0.45] (p=0.0003)* (Figure 18)	6, 1532 vs 1534	
		Subgroup orthopaedic surgery: <u>Statistically significant:</u> MD: -0.90, 95%CI [-1.60;-0.20] (p=0.01)* (Figure 18)	4, 1457 vs 1458	Carson, 1998; Carson, 2011; Grover, 2006; So-Osman, 2013
		Subgroup other surgery: <u>Statistically significant:</u> MD: -1.20, 95%CI [-1.57;-0.83] (p<0.00001)* (Figure 18)	2, 75 vs 76 §	Bush, 1997 (vascular); Markatou, 2012 (abdominal)
Cardiac events		*Overall:* <u>Statistically significant:</u> 116/1420 vs 87/1425 RR: 1.32, 95%CI [1.01;1.72] (p=0.04)* (Figure 19)	4, 1420 vs 1425	
		Subgroup orthopaedic surgery: <u>Statistically significant:</u> 108/1370 vs 79/1376	3,1370 vs 1376	Carson, 2011; Lotke, 1999; So-

		RR: 1.36, 95%CI [1.03;1.80] (p=0.03)* (Figure 19)		Osman, 2013
		Subgroup other surgery: Not statistically significant: 8/50 vs 8/49 § RR: 0.98, 95%CI [0.40;2.40] ¥ (p=0.96)** (Figure 19)	1, 50 vs 49	Bush, 1997 (vascular)
Myocardial infarction		*Overall:* Not statistically significant: 41/1384 vs 27/1382 RR: 1.50, 95%CI [0.93;2.42] ¥ (p=0.09)* (Figure 20)	6, 1384 vs 1382	
		Subgroup orthopaedic surgery: Not statistically significant: 40/1334 vs 25/1333 RR: 1.58, 95%CI [0.97;2.56] ¥ (p=0.07)* (Figure 20)	5, 1334 vs 1333	Carson, 2011; Fan, 2014; Foss, 2009; Grover, 2006; Lotke, 1999
		Subgroup other surgery: Not statistically significant: 1/50 vs 2/49 § RR: 0.49, 95%CI [0.05;5.23] ¥ (p=0.55)** (Figure 20)	1, 50 vs 49	Bush, 1997 (vascular)
Congestive heart failure		*Orthopaedic surgery:* Not statistically significant: 39/1263 vs 30/1263 RR: 1.28, 95%CI [0.80;2.05] ¥ (p=0.30)* (Figure 21)	4, 1263 vs 1263	Carson, 2011; Fan, 2014; Foss, 2009; Parker, 2013
Cerebrovascular accident (CVA) - stroke		*Orthopaedic surgery:* Not statistically significant: 5/1305 vs 13/1301 RR: 0.43, 95%CI [0.16;1.13] ¥ (p=0.09)* (Figure 22)	5, 1305 vs 1301	Carson, 1998; Carson, 2011; Fan, 2014; Foss, 2009; Parker 2013
Sepsis/bacteraemia		*Orthopaedic surgery:* Not statistically significant: 2/399 vs 2/404 RR: 0.96, 95%CI [0.14;6.55] ¥ (p=0.97)* (Figure 23)	2, 399 vs 404	Parker, 2013; So-Osman, 2013
Pneumonia		*Orthopaedic surgery:* Not statistically significant: 84/1778 vs 105/1778 RR: 0.83, 95%CI [0.63;1.09] ¥ (p=0.18)* (Figure 24)	8, 1778 vs 1778	Carson, 1998; Carson, 2011; Fan, 2014; Foss, 2009; Gregersen, 2015; Nielsen, 2014; Parker, 2013; So-

				Osman, 2013
Pneumonia or wound infection		*Orthopaedic surgery:* Not statistically significant: 182/1512 vs 209/1511 RR: 0.76, 95%CI [0.50;1.16] ¥ (p=0.20)* (Figure 25)	4, 1512 vs 1511	Carson, 2011; Foss, 2009; Gregersen, 2015; So-Osman, 2013
Thromboembolism		*Orthopaedic surgery:* Not statistically significant: 12/1604 vs 17/1605 RR: 0.71, 95%CI [0.34;1.47] ¥ (p=0.36)* (Figure 26)	6, 1604 vs 1605	Carson, 1998; Carson, 2011; Fan, 2014; Foss, 2009; Parker, 2013; So-Osman, 2013
Renal failure		*Orthopaedic surgery:* Not statistically significant: 2/194 vs 3/192 RR: 0.73, 95%CI [0.14;3.84] ¥ (p=0.71)* (Figure 27)	2, 194 vs 192	Fan, 2014; Parker, 2013
Mental confusion		*Orthopaedic surgery:* Not statistically significant: 61/668 vs 66/676 RR: 0.92, 95%CI [0.65;1.30] ¥ (p=0.65)* (Figure 28)	6, 668 vs 676	Carson, 2011; Fan, 2014; Foss, 2009; Lotke, 1999; Parker, 2013; So-Osman, 2013
Inability to walk or death at 30 days		*Orthopaedic surgery:* Not statistically significant: 481/1000 vs 459/995 RR: 1.04, 95%CI [0.95;1.14] (p=0.38)** (Figure 29)	1, 1000 vs 995	Carson, 2011
Inability to walk or death at 60 days		*Orthopaedic surgery:* Not statistically significant: 347/1001 vs 351/998 RR: 0.99, 95%CI [0.87;1.11] (p=0.81)** (Figure 30)	1, 1001 vs 998	Carson, 2011
Lower extremity physical activities of daily living at 30 days		*Orthopaedic surgery:* Not statistically significant: 7.4±3.7 vs 7.2±3.6 MD: 0.20, 95%CI [-0.26;0.66] (p=0.39)** (Figure 31)	1, 507 vs 472	Carson, 2011
Lower extremity physical activities of daily living at 60 days		*Orthopaedic surgery:* Not statistically significant: 5.1±4.3 vs 5.1±4.2 MD: 0.00, 95%CI [-0.51;0.51] (p=1.00)** (Figure 32)	1, 553 vs 523	Carson, 2011

Instrumental activities of daily living at 30 days		*Orthopaedic surgery:* Not statistically significant: 3.9±0.4 vs 3.9±0.5 MD: 0.00, 95%CI [-0.06;0.06] (p=1.00)** (Figure 33)	1, 450 vs 437	Carson, 2011
Instrumental activities of daily living at 60 days		*Orthopaedic surgery:* Not statistically significant: 3.7±0.9 vs 3.7±0.8 MD: 0.00, 95%CI [-0.12;0.12] (p=1.00)** (Figure 34)	1, 411 vs 389	Carson, 2011
Energy/fatigue at 30 days		*Orthopaedic surgery:* Not statistically significant: 38.6±7.6 vs 38.7±7.7 MD: -0.1, 95%CI [-1.09;0.89] (p=0.84)** (Figure 35)	1, 459 vs 456	Carson, 2011
Energy/fatigue at 60 days		*Orthopaedic surgery:* Not statistically significant: 42.3±7.4 vs 41.8±7.3 MD: 0.50, 95%CI [-0.38;1.38] (p=0.27)** (Figure 36)	1, 525 vs 544	Carson, 2011
'Timed up and go' test		*Orthopaedic surgery:* Not statistically significant: 36±0 vs 30±0 Not estimable (Figure 37)	1, 25 vs 28 §	Nielsen, 2014

Mean ± SD (unless otherwise indicated)
CI: confidence interval, RR: relative risk, MD: mean difference, IQR: interquartile range
* Calculations (MD or RR, 95%CI and p-value) done by the reviewer using Review Manager software
** Calculations (p-value) done by the reviewer using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Forest plots

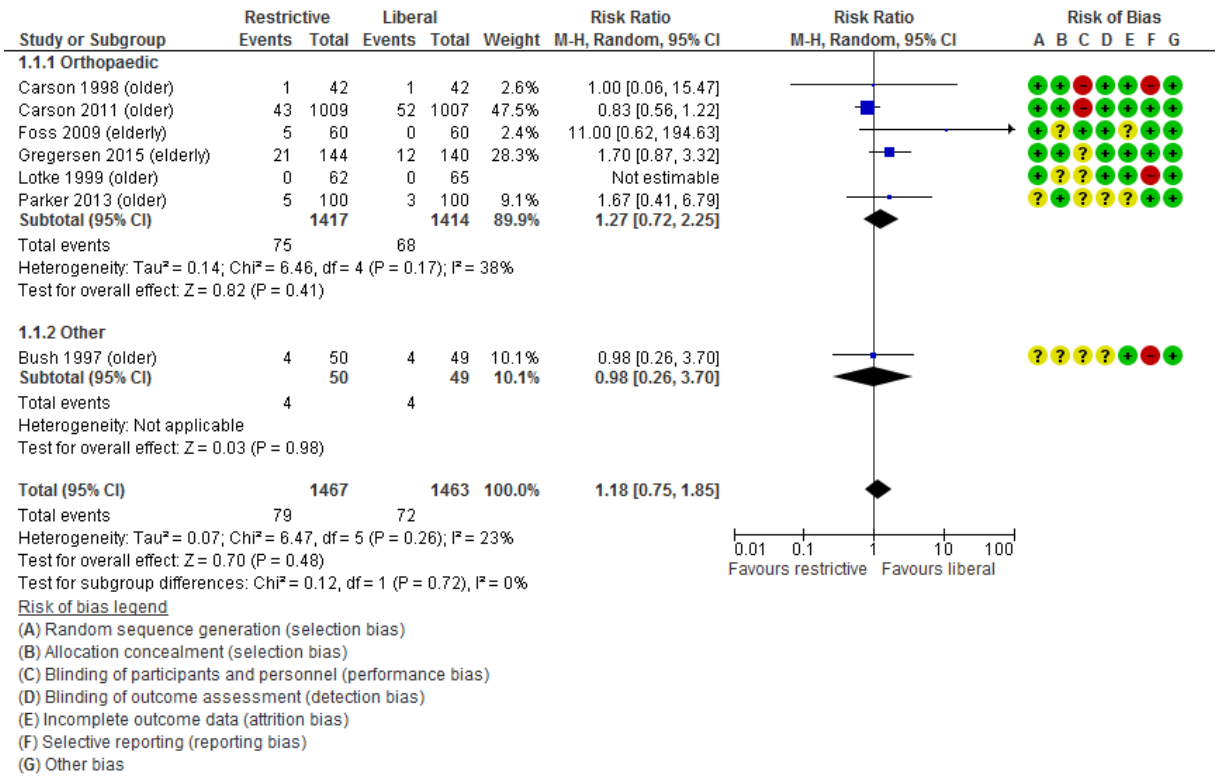


Figure 13: Forest plot of outcome: 30-day mortality.

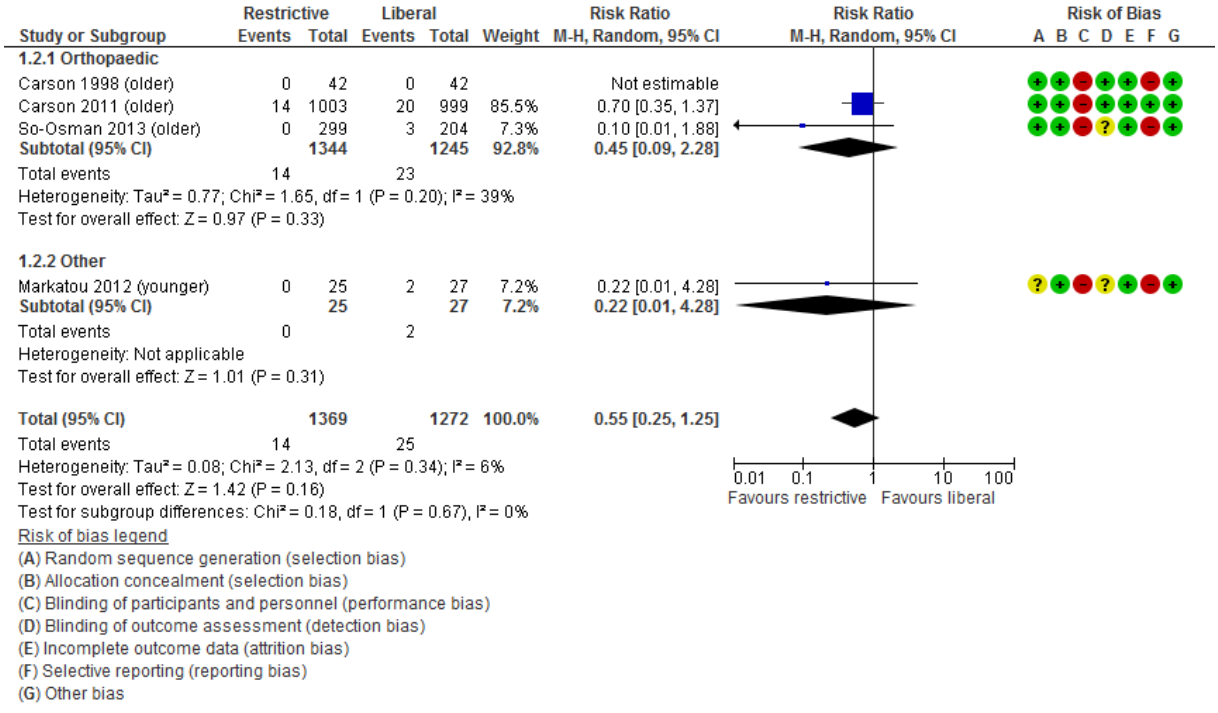


Figure 14: Forest plot of outcome: Hospital mortality.

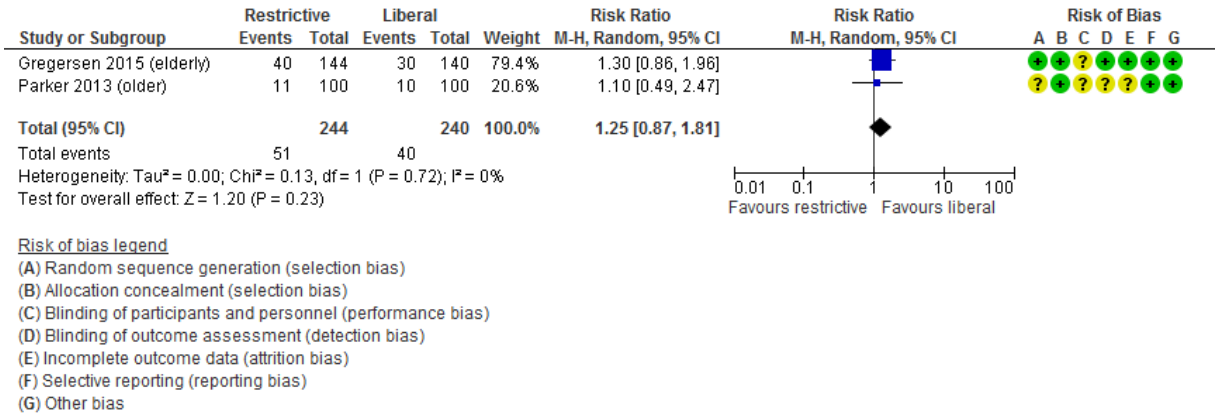


Figure 15: Forest plot of outcome: 90-day mortality.

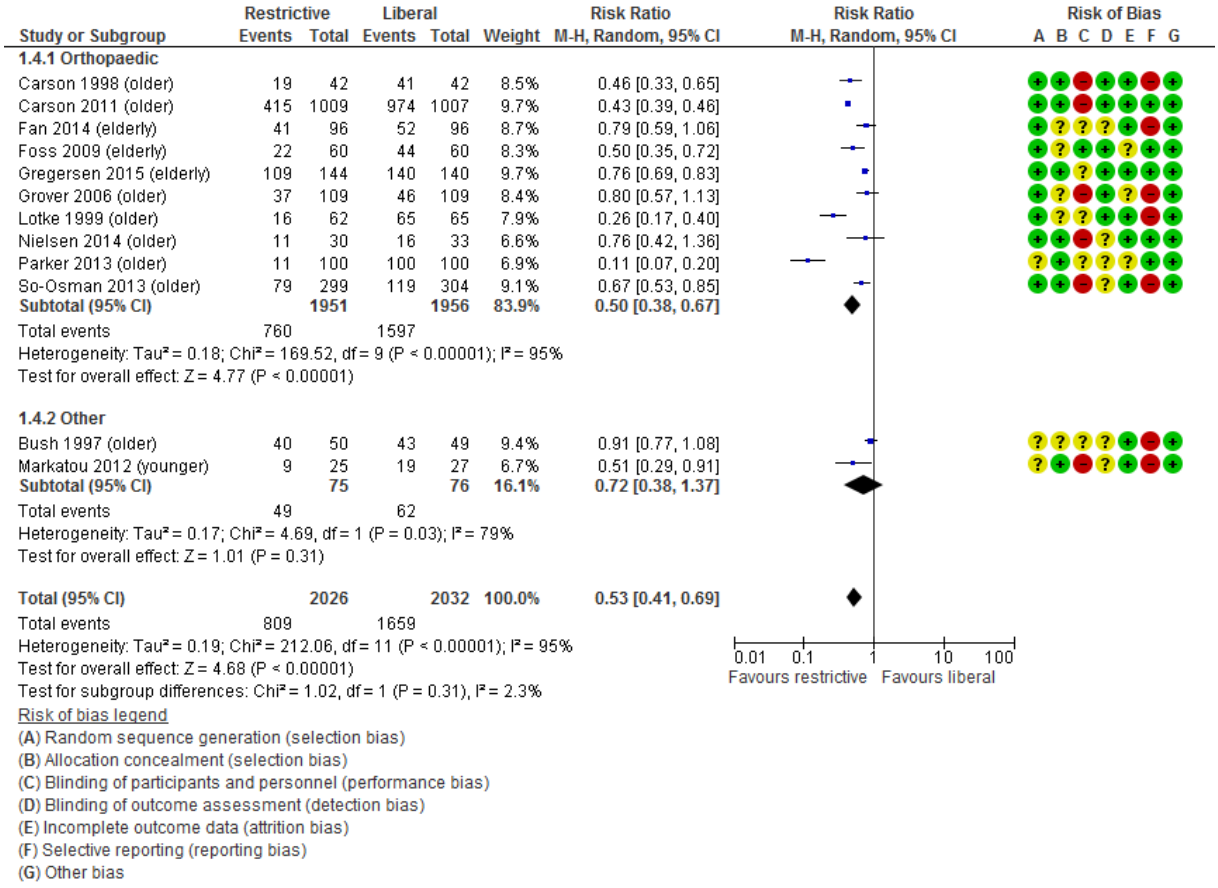


Figure 16: Forest plot of outcome: Participants exposed to blood transfusion.

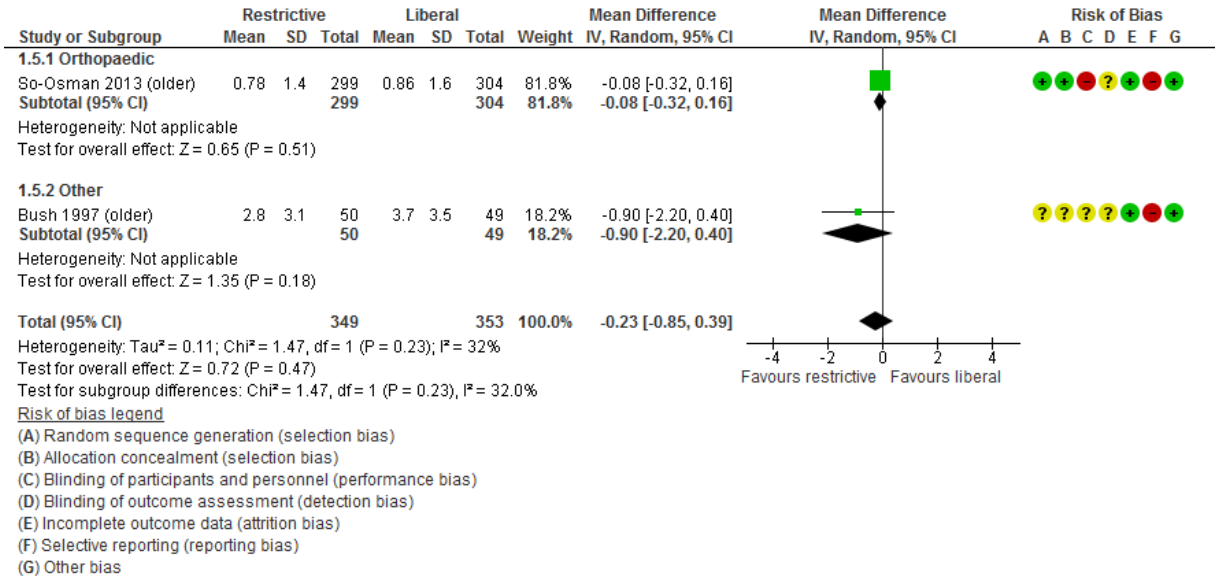


Figure 17: Forest plot of outcome: Units of blood transfused.

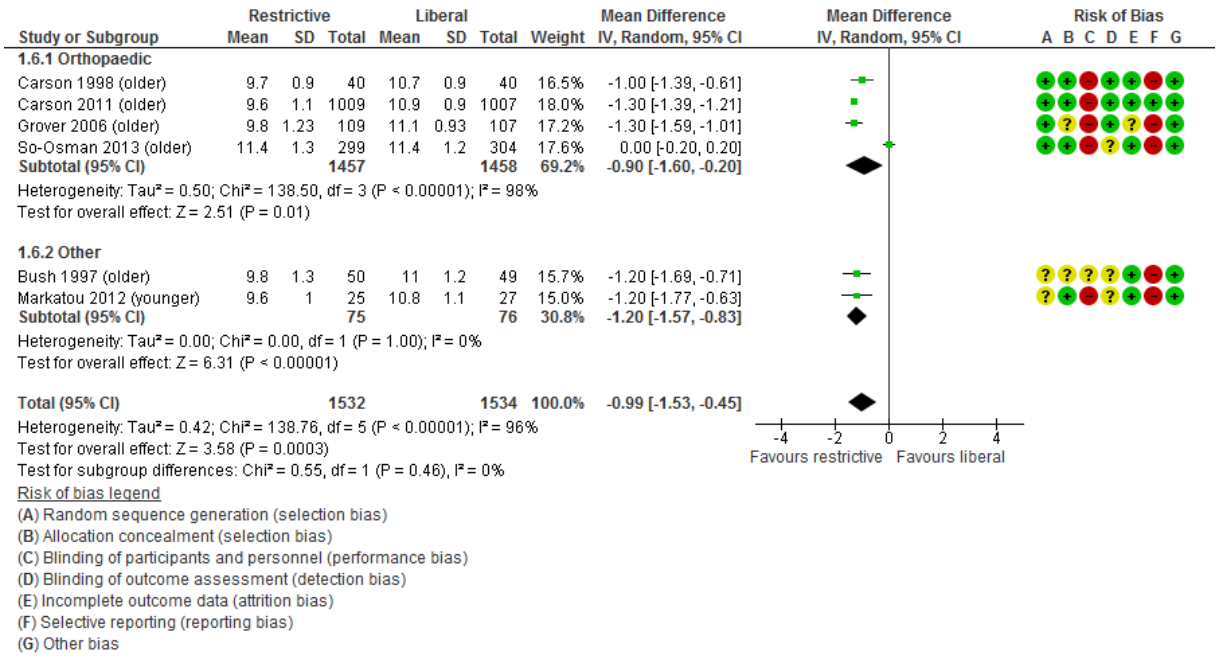


Figure 18: Forest plot of outcome: Haemoglobin concentration.

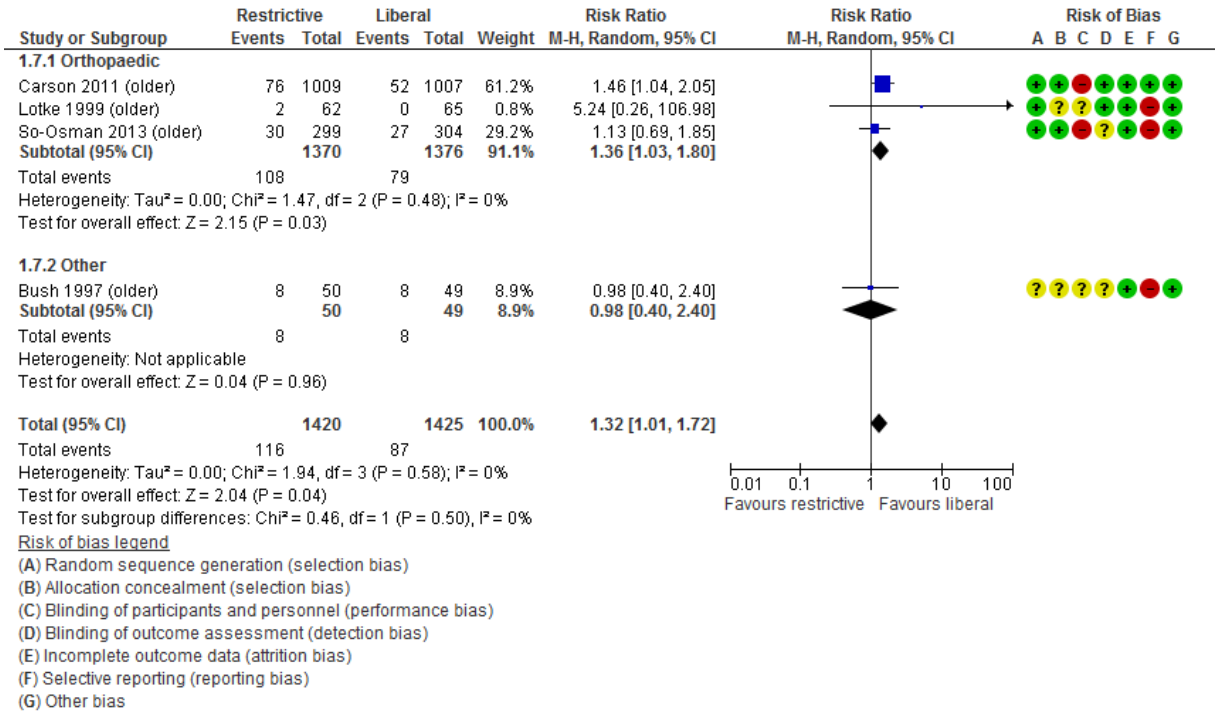


Figure 19: Forest plot of outcome: Cardiac events

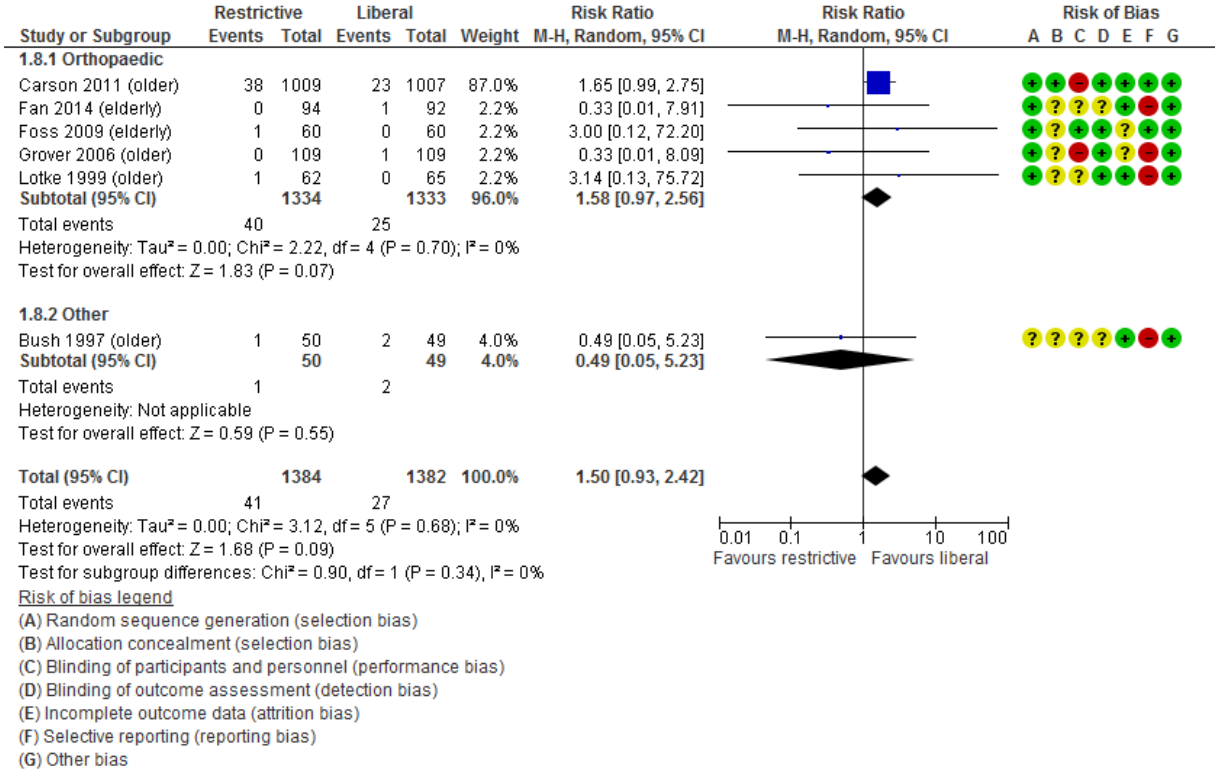


Figure 20: Forest plot of outcome: Myocardial infarction

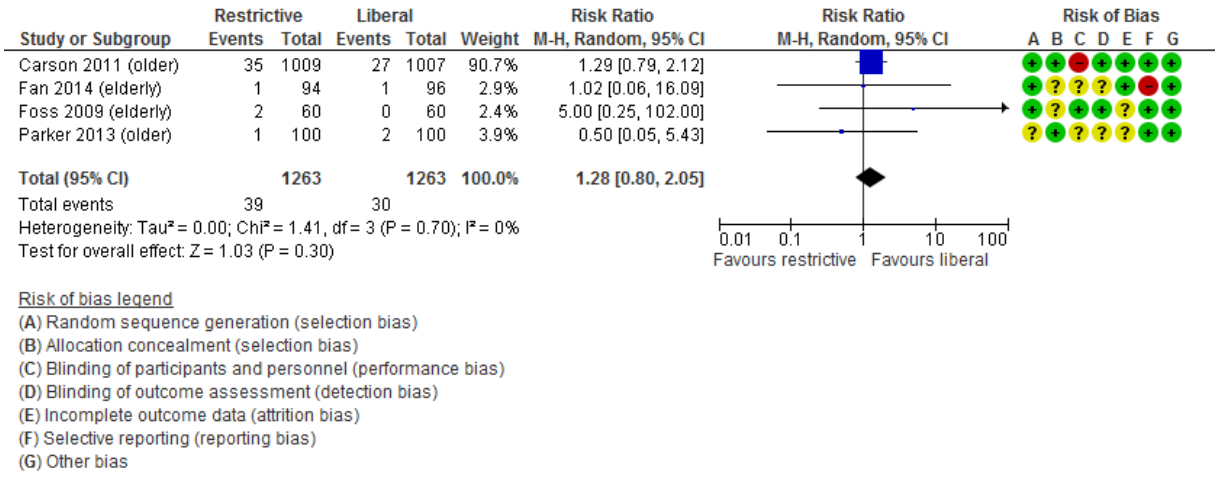


Figure 21: Forest plot of outcome: Congestive heart failure

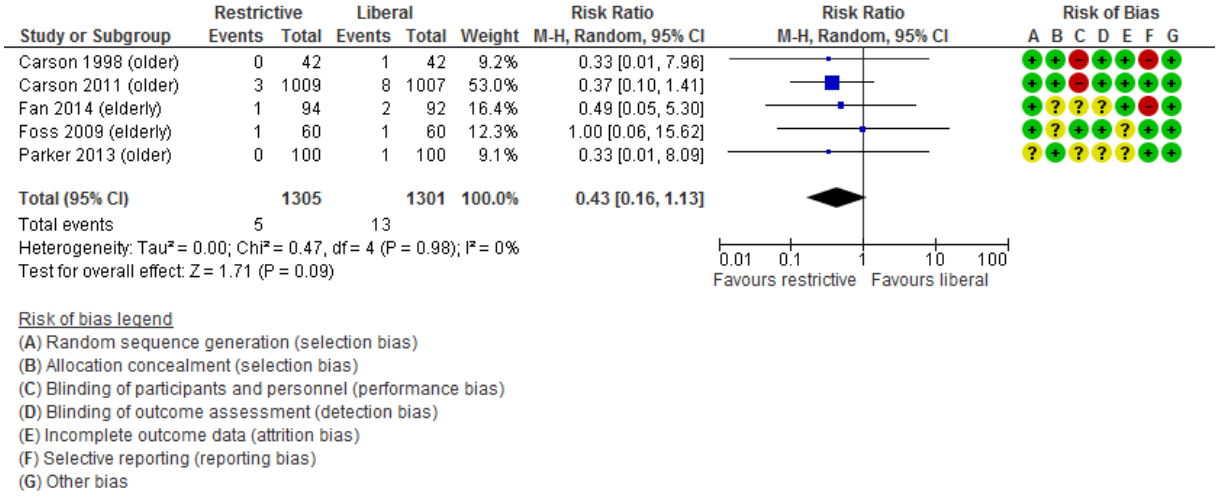


Figure 22: Forest plot of outcome: Cerebrovascular accident (CVA) – stroke

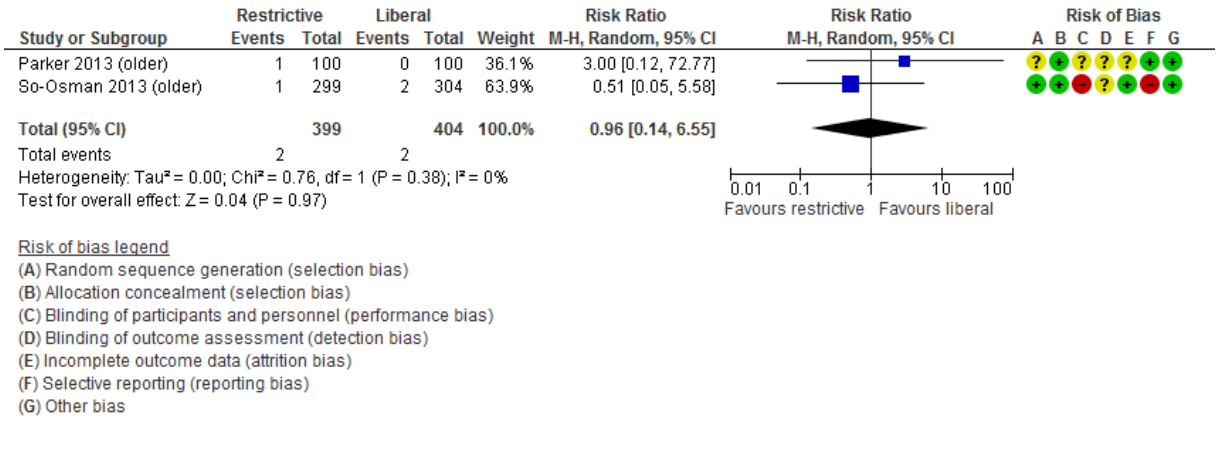
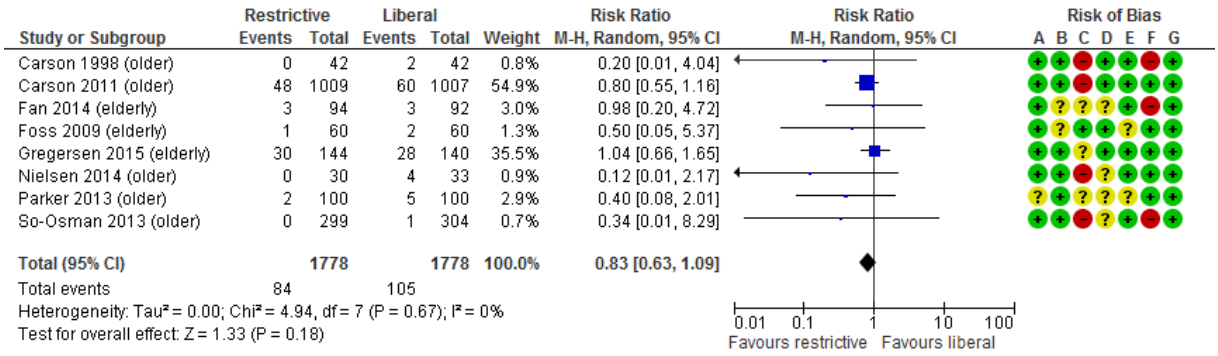
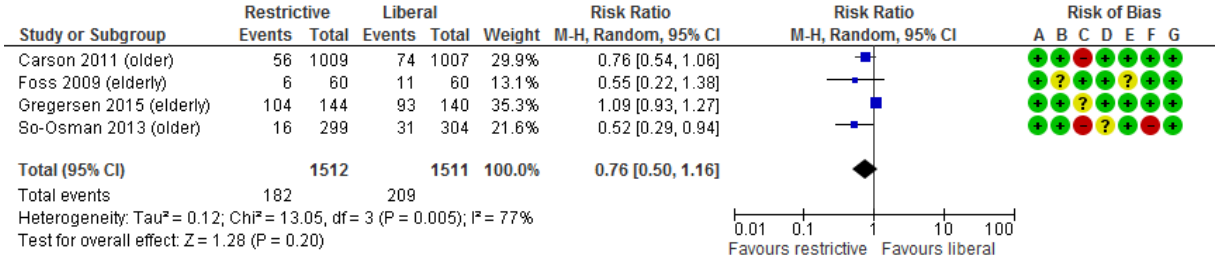


Figure 23: Forest plot of outcome: Sepsis/bacteraemia



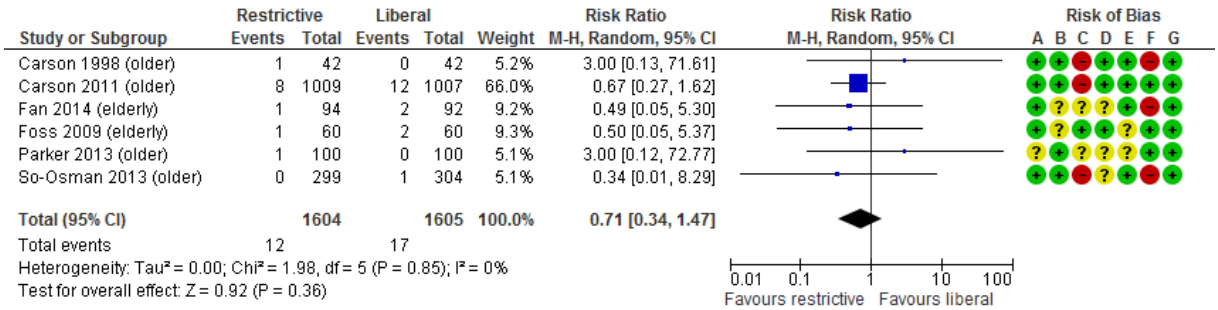
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 24: Forest plot of outcome: Pneumonia



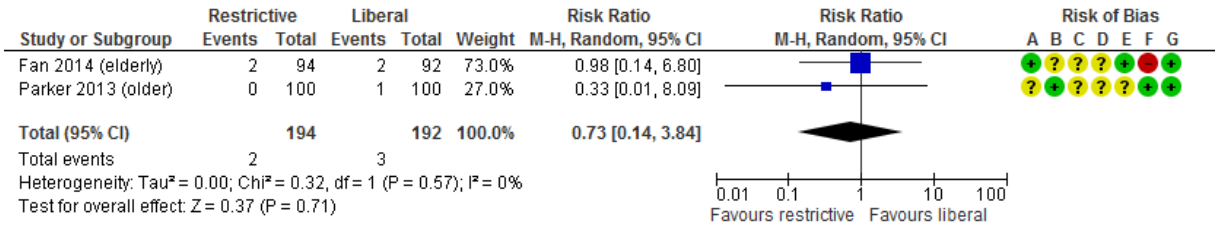
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 25: Forest plot of outcome: Pneumonia or wound infection



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 26: Forest plot of outcome: Thromboembolism



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
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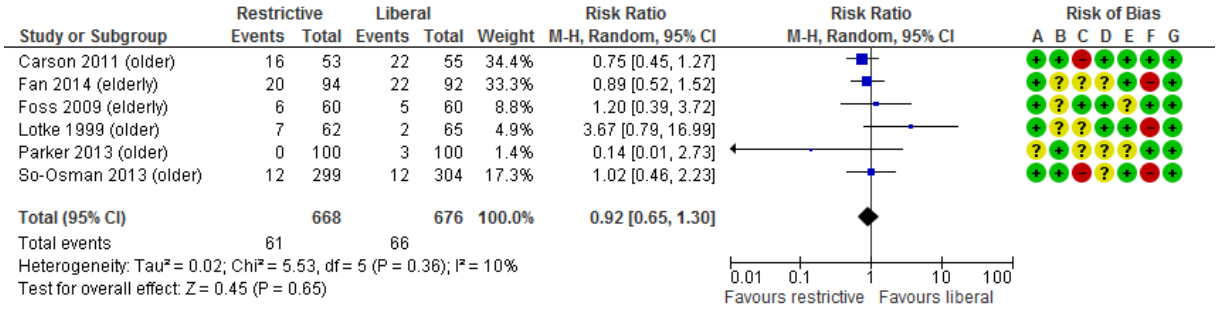
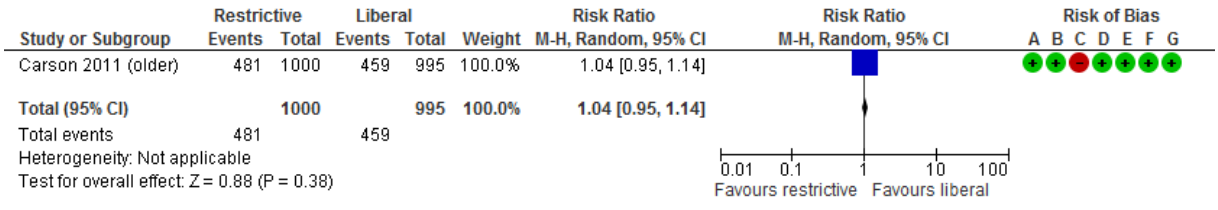
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 27: Forest plot of outcome: Renal failure



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 28: Forest plot of outcome: Mental confusion



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 29: Forest plot of outcome: Inability to walk or death at 30 days

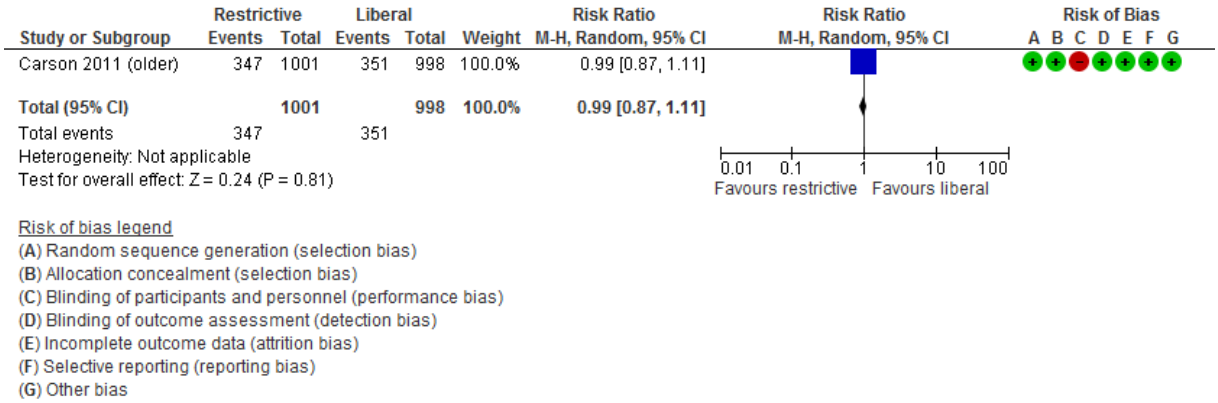


Figure 30: Forest plot of outcome: Inability to walk or death at 60 days

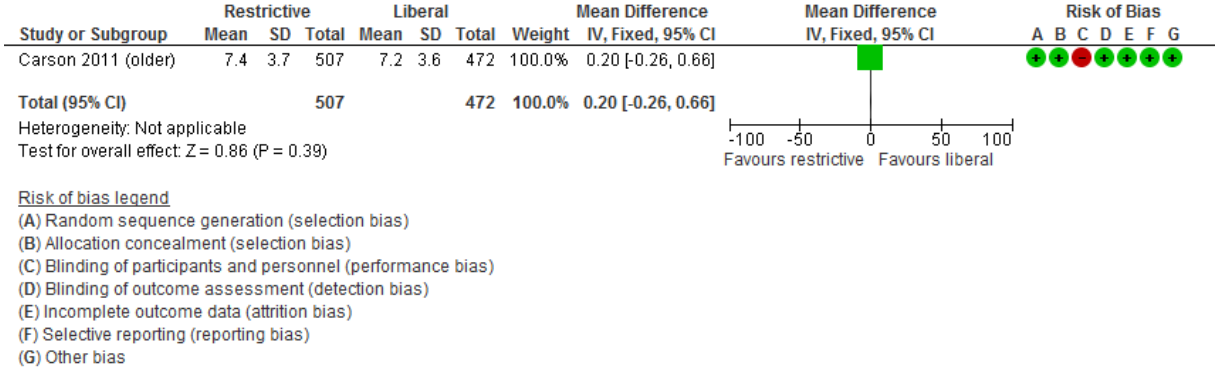


Figure 31: Forest plot of outcome: Lower extremity physical activities of daily living at 30 days

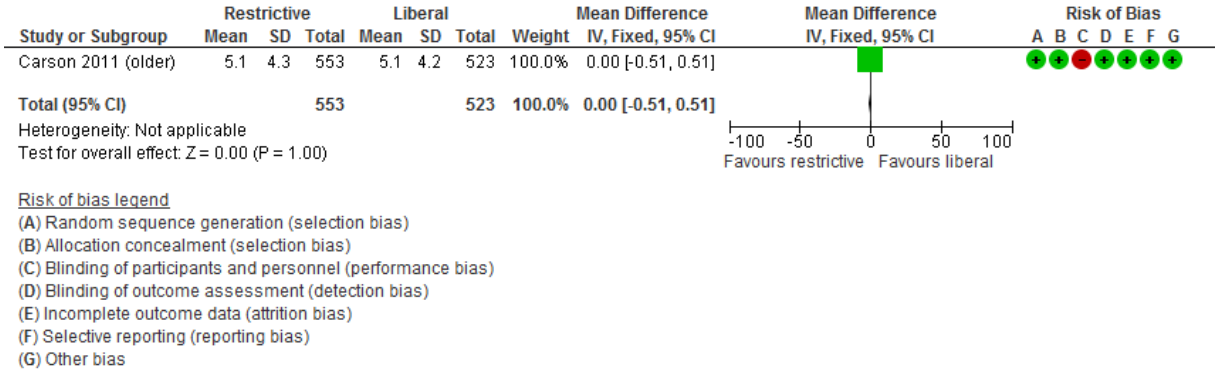


Figure 32: Forest plot of outcome: Lower extremity physical activities of daily living at 60 days

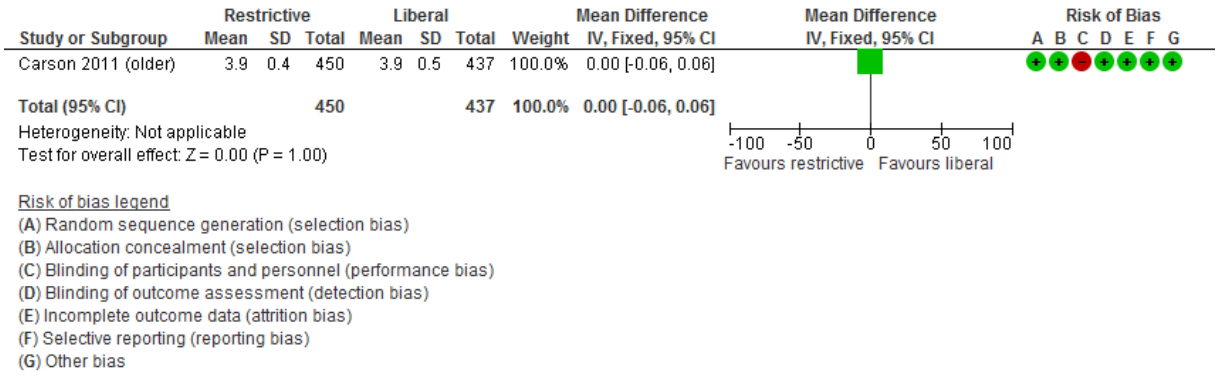


Figure 33: Forest plot of outcome: Instrumental activities of daily living at 30 days

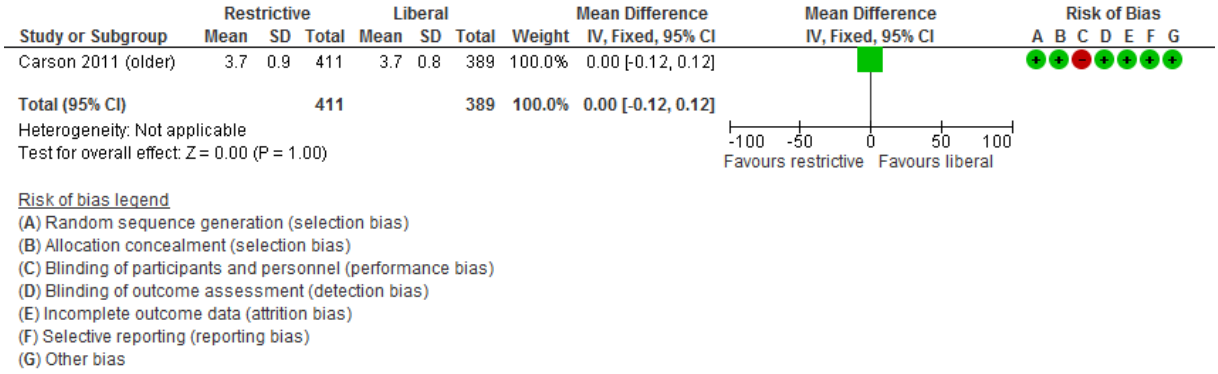


Figure 34: Forest plot of outcome: Instrumental activities of daily living at 60 days

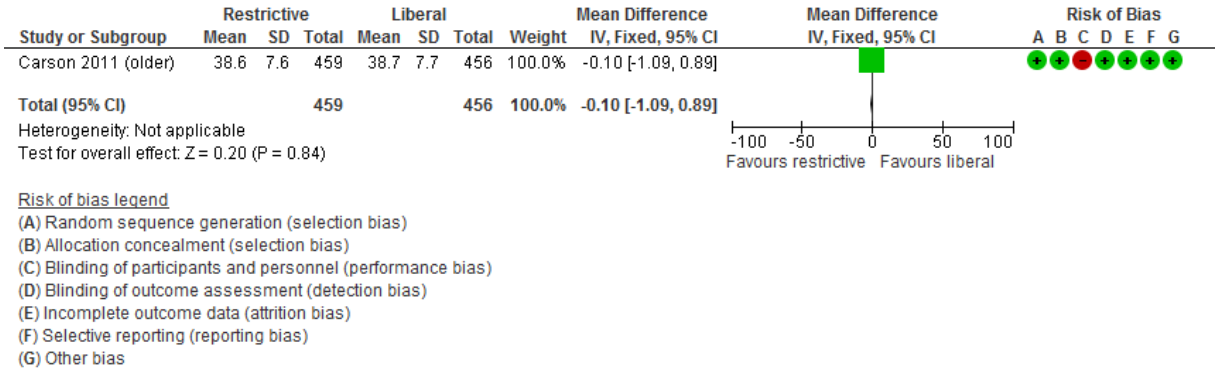


Figure 35: Forest plot of outcome: Energy/fatigue at 30 days

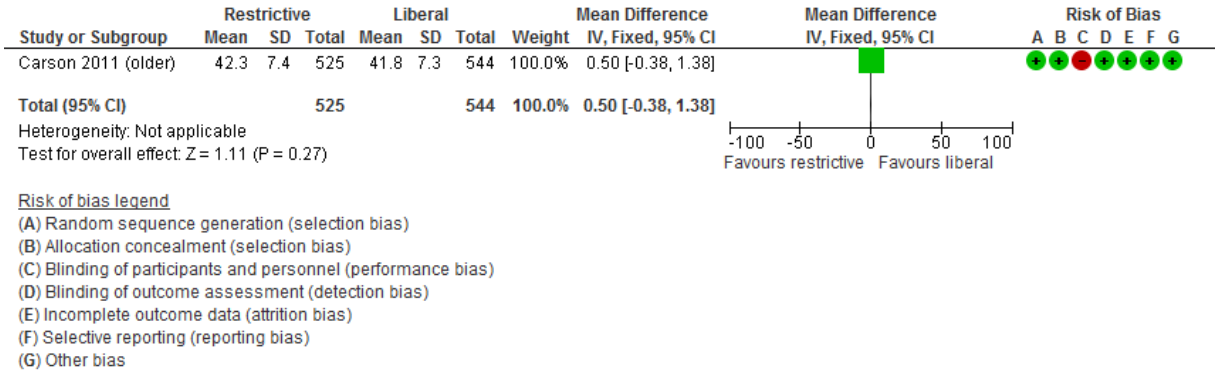


Figure 36: Forest plot of outcome: Energy/fatigue at 60 days

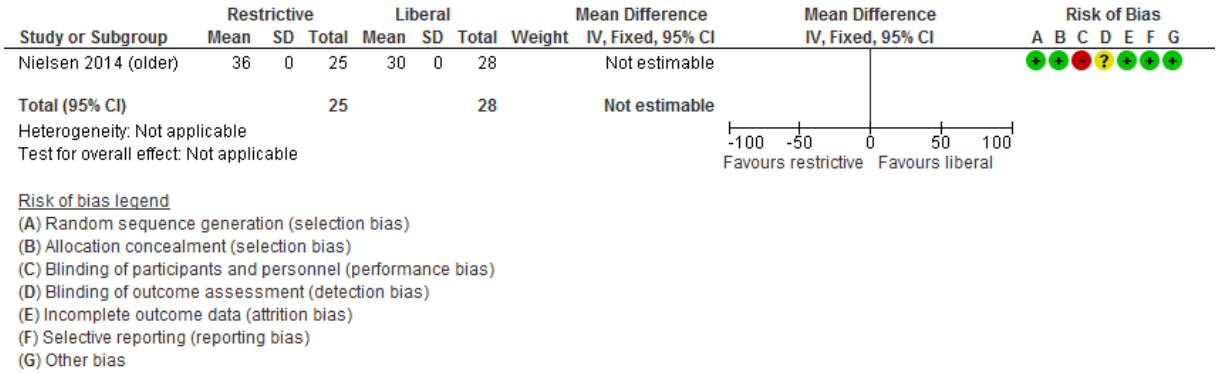


Figure 37: Forest plot of outcome: 'Timed up and go' test

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Bush, 1997	Randomization: Unclear, no information provided. Allocation concealment: Unclear, sealed envelopes were chosen at random for participant assignment.	Participants and personnel: Unclear, both surgeons and anaesthesiologists were informed of the group of randomisation. Outcome assessors: Unclear, no information provided.	No, outcome data appears to be complete.	Yes No pre-registration of study protocol	No
Carson, 1998	Randomization: No, randomisation schedules were stratified by clinical site and cardiovascular disease state. The randomisation was designed in blocks of 2 to 8 participants to avoid imbalance within a site. Allocation concealment: No, study personnel at the clinical sites randomly assigned participants by contacting the data co-ordinating centre's 24-hour automated telephone service.	Participants and personnel: Yes, no blinding of participants or personnel. Outcome assessors: No, primary outcome of mortality allowed a judgement of low risk of bias. Although function was assessed blinded, the morbidity outcomes were not assessed blindly.	No, minimal missing data.	Yes No pre-registration of study protocol	No
Carson, 2011	Randomization: No, data co-ordinating centre staff prepared	Participants and personnel: Yes, after random allocation, clinical site	No, nearly complete reporting data for	No Pre-registration of study protocol @	No

	randomisation schedules for each site using randomly ordered block sizes of 2, 4, 6, or 8. Allocation concealment: No, trial used an automated telephone randomisation system.	staff, clinicians, and participants were not blinded to treatment assignment. Outcome assessors: No, primary and secondary outcomes were assessed blinded to treatment assignment.	primary outcomes and most secondary outcomes.	ClinicalTrials.gov (NCT00071032)	
Fan, 2014	Randomization: No, trial used a random number table. Allocation concealment: Unclear, trial used a sealed envelope technique.	Participants and personnel: Unclear, no information provided. Outcome assessors: Unclear, no information provided.	No, low rate of missing data.	Yes No pre-registration of study protocol	No
Foss, 2009	Randomization: No, a computer-generated list was used. Allocation concealment: Unclear, sealed envelopes were used.	Participants and personnel: No, participants were blinded. Outcome assessors: No, physiotherapist who performed ambulation assessment was blinded	Unclear, 13 of 100 participants did not have ambulation assessment.	No Pre-registration of study protocol @ ClinicalTrials.gov (NCT00162617)	No
Gregersen, 2015	Randomization: No, random sequence generation was not specifically stated, but it was likely since a clinical trial support system was used. Allocation concealment: No, web-based randomisation system with allocation concealment was used.	Participants and personnel: Unclear, participants were blinded but not the clinicians. Outcome assessors: No, assessor was blinded.	No, outcome data appeared to be complete.	No Pre-registration of study protocol @ ClinicalTrials.gov (NCT01102010)	No

Grover, 2006	Randomization: No, random numbers table was used. Allocation concealment: Unclear, sealed envelopes were used.	Participants and personnel: Yes, anaesthetists and surgical team responsible for treatment were aware of allocation. Outcome assessors: No, outcome assessment was blind.	Unclear, of a recruited 260 participants, outcome data were presented for 218. The missing 42 participants did not have analysable tape recordings.	Yes No pre-registration of study protocol	No
Lotke, 1999	Randomization: No, trial used a computer random number generator. Allocation concealment: Unclear, no information provided.	Participants and personnel: Unclear, no information provided. Outcome assessors: No, assessments were made by a person blind to the group to which the participant was assigned.	No, outcome data appear to have been complete.	Yes No pre-registration of study protocol	No
Markatou, 2012	Randomization: Unclear, randomization was done by means of sealed opaque envelopes containing odd and even numbers. Allocation concealment: No, sealed opaque envelopes were used.	Participants and personnel: Yes, the surgical team and the anesthesiologist responsible for the patient were aware of the study protocol and group assignment. Outcome assessors: Unclear, no information provided.	No, no loss to follow-up reported.	Yes No pre-registration of study protocol	No
Nielsen, 2014	Randomization: No, a dedicated computer program (Idefix) was used after entering participants' baseline data. The allocation was written on a form, which was kept in the investigator's office, and the allocation could	Participants and personnel: Yes, the allocation and Hb during the testing period were concealed from the participants but the investigator, the staff in the operating room, and the staff at the ward could not be blinded. Outcome assessors:	No	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT00906295)	No

	only be accessed by the investigator in charge of administrating red blood cells. Allocation concealment: No, only 1 investigator had access to the programme. Investigators at the other hospital had to call this investigator to randomise.	Unclear, the physiotherapist testing the participant was blinded, but it was not stated who reviewed medical records for other outcomes.			
Parker, 2013	Randomization: Unclear, no information provided. Allocation concealment: No, trial used opaque numbered envelopes.	Participants and personnel: Unclear, no information provided. Outcome assessors: Unclear, no information provided.	Unclear, mobility score was missing for 94 of 200 participants.	No Pre-registration of study protocol (ISRCTN61328173)	No
So-Osman, 2013	Randomization: No, post-hoc analysis of an earlier randomized trial in which patients were stratified (using blocks of variable length) according to hospital, type of surgery and risk group. Randomization was achieved using a uniform distribution for a pregenerated list of sufficient length. Allocation concealment:	Participants and personnel: Yes, clinicians caring for the participants were aware of allocation status. There was no blinding information on participants. Outcome assessors: Unclear, no information provided.	No	Yes No pre-registration of study protocol	No

	No, research nurse opened sealed opaque envelopes.				

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **Bush 1997** Bush RL, Pevec WC, Holcroft JW. *A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients*. Am J Surg 1997, 174(2):143–148. **Carson 1998** Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, et al. *A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture*. Transfusion 1998, 38(6): 522–529. **Carson 2011** Carson JL, Sieber F, Cook DR, Hoover DR, Noveck H, Chaitman BR, et al. *Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial.* Lancet 2015, 385(9974):1183–9. *Carson JL, TerrinML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. *Liberal or restrictive transfusion in high-risk patients after hip surgery*. N Engl J Med 2011, 365(26):2453–2462. Gruber-Baldini AL, Marcantonio E, Orwig D, Magaziner J, Terrin M, Barr E, et al. *Delirium outcomes in a randomized trial of blood transfusion thresholds in hospitalized older adults with hip fracture*. J Am Geriatr Soc 2013, 61(8):1286–95. **Fan 2014** Fan YX, Liu FF, Jia M, Yang JJ, Shen JC, Zhu GM, et al. *Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: a preliminary study*. Arch Gerontol Geriatr 2014, 59(1):181–185. **Foss 2009** Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. *The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery*. Transfusion 2009, 49(2):227–234. **Gregersen 2015** Gregersen M, Borris LC, Damsgaard EM. *Blood transfusion and overall quality of life after hip fracture in frail elderly patients--the transfusion requirements in frail elderly randomized controlled trial.* J Am Med Dir Assoc 2015, 16(9):762–6. *Gregersen M, Borris LC, Damsgaard EM. *Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: the TRIFE randomized controlled trial.* Acta Orthop 2015, 86(3):363–372. Gregersen M, Damsgaard EM, Borris LC. *Blood transfusion and risk of infection in frail elderly after hip fracture surgery: the TRIFE randomized controlled trial.* Eur J Orthop Surg Traumatol 2015;25(6):1031–8. **Grover 2006** *Grover M, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, et al. *Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty*. Vox Sang 2006, 90(2):105–112. Grover M, Talwalker SA, Contreras, Soni N. *Blood transfusion threshold and silent myocardial ischemia after lower limb arthroplasty: a randomized controlled trial of*

	transfusion strategy. Transfusion Alternatives in Transfusion Medicine 2005;7(1 (Suppl)):62–3. **Lotke 1999** Lotke PA, Barth P, Garino JP, Cook EF. *Predonated autologous blood transfusions after total knee arthroplasty: immediate versus delayed administration*. J Arthroplasty 1999, 14(6):647–650. **Markatou 2012** Markatou M, Theodoraki K, Rizos D and Fassoulaki A. *Targeting perioperative hemoglobin in major abdominal surgery*. J Anesthe Clinic Res 2012, 3:190 doi: 10.4172/2155-6148.1000190. Identified from Hovaguimian 2016. **Nielsen 2014** Nielsen K, Johansson PI, Dahl B, Wagner M, Frausing B, Børglum J, et al. *Perioperative transfusion threshold and ambulation after hip revision surgery--a randomized trial*. BMC Anesthesiol 2014, 14:89. **Parker 2013** Parker MJ. *Randomised trial of blood transfusion versus a restrictive transfusion policy after hip fracture surgery*. Injury 2013;44(12):1916–1918. **So-Osman 2013** So-Osman C. *A restrictive transfusion trigger is a method for blood saving in elective orthopaedic surgery*. Vox Sang 2004, 87(Suppl 3):52. *So-Osman C, Nelissen R, Brand R, Faber F, Slaa RT, Stiggelbout A, et al. *The impact of a restrictive transfusion trigger on post-operative complication rate and well-being following elective orthopaedic surgery: a post-hoc analysis of a randomised study*. Blood Transfus 2013, 11(2):289–295. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. Vox Sang 2010, 98(1):56–64. **<u>Systematic reviews</u>** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Hovaguimian F, Myles PS. *Restrictive versus Liberal Transfusion Strategy in the Perioperative and Acute Care Settings: A Context-specific Systematic Review and Meta-analysis of Randomized Controlled Trials.* Anesthesiology. 2016, 125(1):46-61. Identified in search update. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease*. In peer-review [February 2018]. *Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 6: RBC transfusion triggers in adult acute (gastrointestinal) bleeding patients

Overview evidence table GRADE software (PICO 6)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
30-day mortality												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	33/699 (4.7%)	61/823 (7.4%)	**RR 0.65** (0.43 to 0.97)	**26 fewer per 1.000** (from 2 fewer to 42 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospital mortality												
1	randomised trials	serious [a]	not serious	serious [c]	serious [b]	none	0/26 (0.0%)	2/24 (8.3%)	**RR 0.19** (0.01 to 3.67)	**68 fewer per 1.000** (from 82 fewer to 222 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patients exposed to RBC transfusion												
4	randomised trials	serious [a]	not serious	not serious	not serious	none	365/885 (41.2%)	665/1012 (65.7%)	**RR 0.55** (0.41 to 0.75)	**296 fewer per 1.000** (from 164 fewer to 388 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
RBC units transfused												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
3	randomised trials	serious [a]	not serious	not serious	not serious	none	873	1002	-	MD **1.79 units lower** (3 lower to 0.58 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Haemoglobin concentration												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	647	725	-	MD **0.89 lower** (1.01 lower to 0.77 lower)	⊕⊕◯◯ LOW	IMPORTANT
Myocardial infarction												
1	randomised trials	serious [d]	not serious	not serious	serious [b]	none	8/444 (1.8%)	13/445 (2.9%)	**RR 0.62** (0.26 to 1.47)	**11 fewer per 1.000** (from 14 more to 22 fewer)	⊕⊕◯◯ LOW	CRITICAL
Congestive heart failure												
1	randomised trials	serious [d]	not serious	not serious	serious [b]	none	12/444 (2.7%)	21/445 (4.7%)	**RR 0.57** (0.29 to 1.15)	**20 fewer per 1.000** (from 7 more to 34 fewer)	⊕⊕◯◯ LOW	IMPORTANT
CVA-stroke												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [d]	not serious	not serious	serious [b]	none	3/444 (0.7%)	6/445 (1.3%)	**RR 0.50** (0.13 to 1.99)	**7 fewer per 1.000** (from 12 fewer to 13 more)	⊕⊕◯◯ LOW	CRITICAL
Rebleeding												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	55/727 (7.6%)	104/852 (12.2%)	**RR 0.54** (0.31 to 1.99)	**56 fewer per 1.000** (from 84 fewer to 121 more)	⊕⊕◯◯ LOW	IMPORTANT
Pneumonia												
1	randomised trials	serious [d]	not serious	not serious	very serious [b]	none	43/444 (9.7%)	48/445 (10.8%)	**RR 0.90** (0.61 to 1.33)	**11 fewer per 1.000** (from 36 more to 42 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Pneumonia or wound infection												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	186/701 (26.5%)	227/828 (27.4%)	**RR 0.96** (0.79 to 1.17)	**11 fewer per 1.000** (from 47 more to 58 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Renal failure												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7-8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [d]	not serious	not serious	serious [b]	none	78/444 (17.6%)	97/445 (21.8%)	**RR 0.81** (0.62 to 1.05)	**41 fewer per 1.000** (from 11 more to 83 fewer)	⊕⊕◯◯ LOW	CRITICAL
Function and fatigue (EQ-5D)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	176	139	-	MD **0.07 points higher** (0 to 0.14 higher)	⊕⊕◯◯ LOW	IMPORTANT
30-day mortality (subgroup: patients with cirrhosis)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	15/139 (10.8%)	25/138 (18.1%)	**RR 0.60** (0.33 to 1.08)	**72 fewer per 1.000** (from 14 more to 121 fewer)	⊕⊕◯◯ LOW	CRITICAL
Rebleeding (subgroup: patients with cirrhosis)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	16/139 (11.5%)	31/138 (22.5%)	**RR 0.51** (0.29 to 0.89)	**110 fewer per 1.000** (from 25 fewer to 159 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; a. see risk of bias items in forest plots or quality of evidence table; b. Limited sample size, low number of events and/or large variability of the results; c. study from the 1980s, not generalizible to the 2018 context; d. Detection bias (outcome assessors were not blinded)

Detailed evidence summary (PICO 6)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with an acute gastrointestinal bleeding (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. <u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6 **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 **Embase** (via Embase.com interface) using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 **Transfusion evidence library** (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: patients with an acute gastrointestinal bleeding. **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary:* Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue.

	Study design: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) (cluster) randomized controlled trials identified in the update. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Blair, 1986, UK	Randomised controlled trial	50 consecutive participants with severe upper gastrointestinal haemorrhage (clinical specialty subgroup (Carson, 2016): acute blood loss/trauma) Restrictive group: n=26, male/female ratio=2:1, age=60±17.8 years Liberal group: n=24, male/female ratio=2:1, age=64±17.6 years	Restrictive group (intervention): not transfused unless the Hb <8.0 g/dL or shock persisted after initial resuscitation with Haemaccel Liberal group (control): at least 2 units of red blood cells during their first 24 hours in hospital Transfusion: units of blood	Financial assistance from Crawley and Jersey Research Fund. Identified from the systematic review of Carson et al., 2016.
Fisher, 1956, United Kingdom	Experimental: randomised controlled trial	22 trauma participants were randomly allocated to 1 of 2 groups: • Liberal group: n = 10 • Restrictive group: n = 12 NB: no demographic data were reported.	Restrictive RBC transfusion trigger: an attempt was made to leave the RBC volume at the end of resuscitation at 70% to 80% of normal. Liberal RBC transfusion trigger: the aim was to achieve 100% or more of the RBC volume at	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

			the end of resuscitation.	
Jairath, 2015, UK	Cluster-randomised controlled trial	936 participants with upper gastrointestinal bleeding in 6 hospitals (clinical specialty subgroup (Carson, 2016): acute blood loss/trauma) Restrictive group: n=403, 244 males and 159 females, age=58.0±20.3 years Liberal group: n=533, 322 males and 211 females, age=60.4±20.0 years	Restrictive group (intervention): transfusion if Hb<8 g/dL, post-transfusion target of 8.1–10.0 g/dL Liberal group (control): transfusion if Hb<10 g/dL threshold, post-transfusion Hb target of 10.1–12.0 g/dL Transfusion: RBC tranfusion	Government funded and run clinical trial. Identified from the systematic review of Carson et al., 2016.
Villanueva, 2013, Spain	Randomised controlled trial	889 participants with haematemesis and/or melena due to upper GI bleeding (clinical specialty subgroup (Carson, 2016): acute blood loss/trauma) Restrictive group: n=444, 291 males and 154 females, age=66±15 years Liberal group: n=445, 314 males and 130 females, age=64±16 years	Restrictive group (intervention): transfusion if Hb<7 g/dL target range for the post-transfusion Hb level of 7-9 g/dL Liberal group (control): transfusion if Hb<9 g/dL target range for the post-transfusion Hb level of 9-11 g/dL Transfusion: prestorage leukocyte reduced units of red cells	Research funded by foundation connected to hospital. One author divulged receiving consulting fees from industry. Identified from the systematic review of Carson et al., 2016.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcomes				
30-day mortality	Restrictive vs liberal transfusion threshold	Statistically significant: 33/699 vs 61/823 § RR: 0.65, 95%CI [0.43;0.97] (p=0.037) (Figure 38) *In favour of restrictive transfusion threshold*	3, 699 vs 823	Blair, 1986; Jairath, 2015; Villanueva, 2013

30-day mortality (subgroup: patients with cirrhosis)		Not Statistically significant: 15/139 vs 25/138 § RR: 0.60, 95%CI [0.33;1.08] (p=0.09)	1, 139 vs 138	Villanueva, 2013
Hospital mortality		Not statistically significant: 0/26 vs 2/24 § RR: 0.19, 95%CI [0.01;3.67] ¥ (p=0.27)* (Figure 39)	1, 26 vs 24	Blair, 1996
Participants exposed to blood transfusion		Statistically significant: 365/885 vs 665/1012 RR: 0.58, 95%CI [0.45;0.75] (p<0.0001)** (Figure 40) *In favour of restrictive transfusion threshold*	4, 885 vs 1012	Blair, 1986; Fisher 1956; Jairath, 2015; Villanueva, 2013
Units of blood transfused		Statistically significant: MD: -1.79; 95%CI [-3.00; -0.58] (p=0.004)** (Figure 41) *In favour of restrictive transfusion threshold*		
Secondary outcomes				
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	Statistically significant: MD: -0.89; 95%CI [-1.01;-0.77] (p<0.00001)** (Figure 42)	3, 647 vs 725	Blair, 1986; Jairath, 2015; Villanueva, 2013
Myocardial infarction		Not statistically significant: 8/444 vs 13/445 § RR: 0.62, 95%CI [0.26;1.47] ¥ (p=0.28)* (Figure 43)	1, 444 vs 445	Villanueva, 2013
Congestive heart failure		Not statistically significant: 12/444 vs 21/445 § RR: 0.57, 95%CI [0.29;1.15] ¥ (p=0.12)* (Figure 44)		
Cerebrovascular accident (CVA) - stroke		Not statistically significant: 3/444 vs 6/445 § RR: 0.50, 95%CI [0.13;1.99] ¥ (p=0.33)* (Figure 45)		
Rebleeding		Statistically significant: 55/727 vs 104/852 § RR: 0.54, 95%CI [0.31;0.93] (p=0.03)** (Figure 46) *In favour of restrictive transfusion threshold*	3, 727 vs 852	Blair, 1986; Jairath, 2015; Villanueva, 2013
Rebleeding (subgroup: patients with cirrhosis)		Statistically significant: 16/139 vs 31/138 § RR: 0.51, 95%CI [0.29;0.89] (p=0.02) *In favour of restrictive transfusion threshold*	1, 139 vs 138	Villanueva 2013
Pneumonia		Not statistically significant: 43/444 vs 48/445 § RR: 0.90, 95%CI [0.61;1.33] ¥ (p=0.59)* (Figure 47)	1, 444 vs 445	Villanueva, 2013

Pneumonia or wound infection		Not statistically significant: 186/701 vs 227/828 RR: 0.96, 95%CI [0.79;1.17] (p=0.69)** (Figure 48)	2, 701 vs 828	Jairath, 2015; Villanueva, 2013
Renal failure		Not statistically significant: 78/444 vs 97/445 § RR: 0.81, 95%CI [0.62;1.05] ¥ (p=0.11)* (Figure 49)	1, 444 vs 445	Villanueva, 2013
Function and fatigue (EuroQol (EQ-5D))		Statistically significant: 0.76±0.27 vs 0.69±0.32 MD: 0.07, 95%CI [0.00;0.14] (p=0.04)* (Figure 50) *In favour of restrictive transfusion threshold*	1, 176 vs 139 §	Jairath, 2015

Mean ± SD (unless otherwise indicated)
CI: confidence interval, RR: relative risk, MD: mean difference
* Calculations (p-value) done by the reviewer(s) using Review Manager software
** Calculations (RR or MD, 95%CI and p-value) done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Forest plots

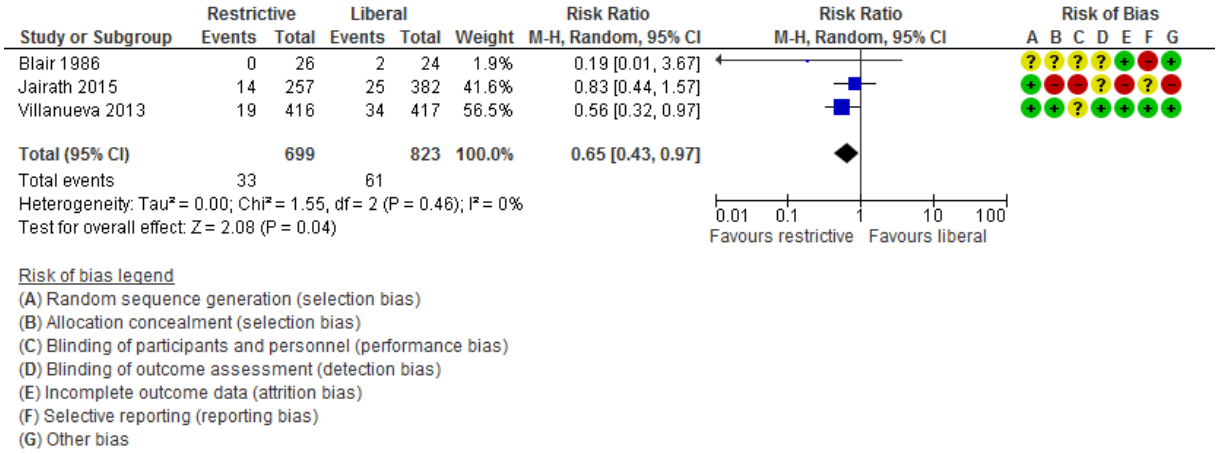


Figure 38: Forest plot of outcome: 30-day mortality.

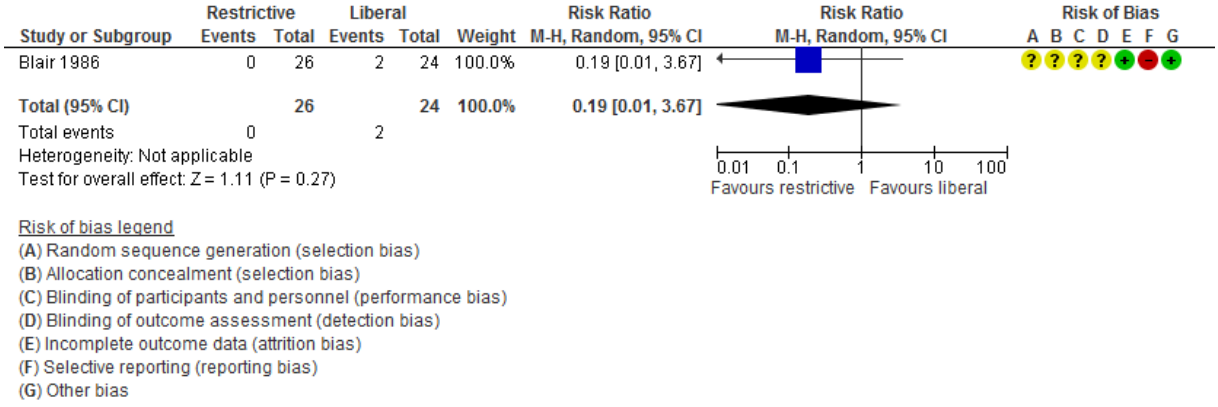


Figure 39: Forest plot of outcome: Hospital mortality.

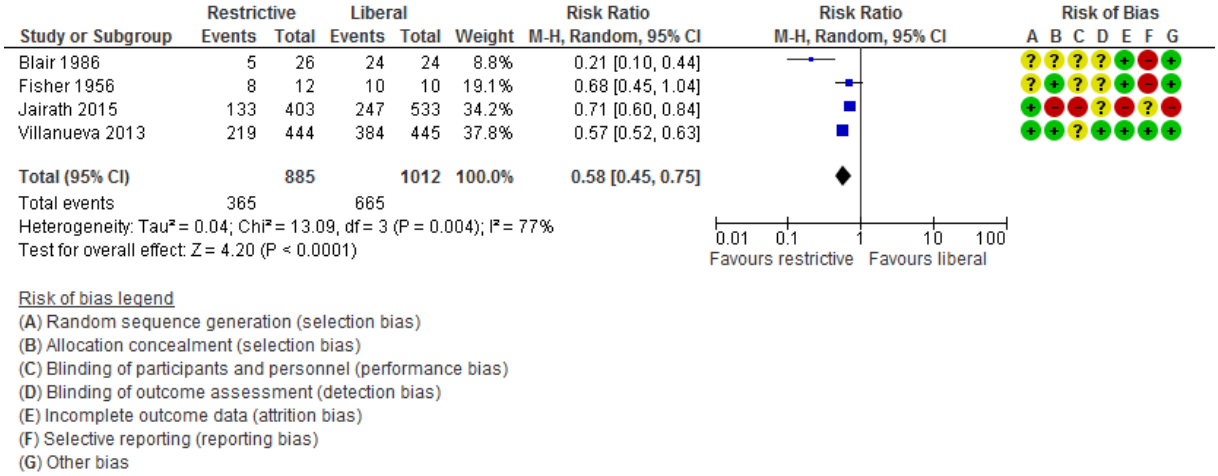


Figure 40: Forest plot of outcome: Participants exposed to blood transfusion.

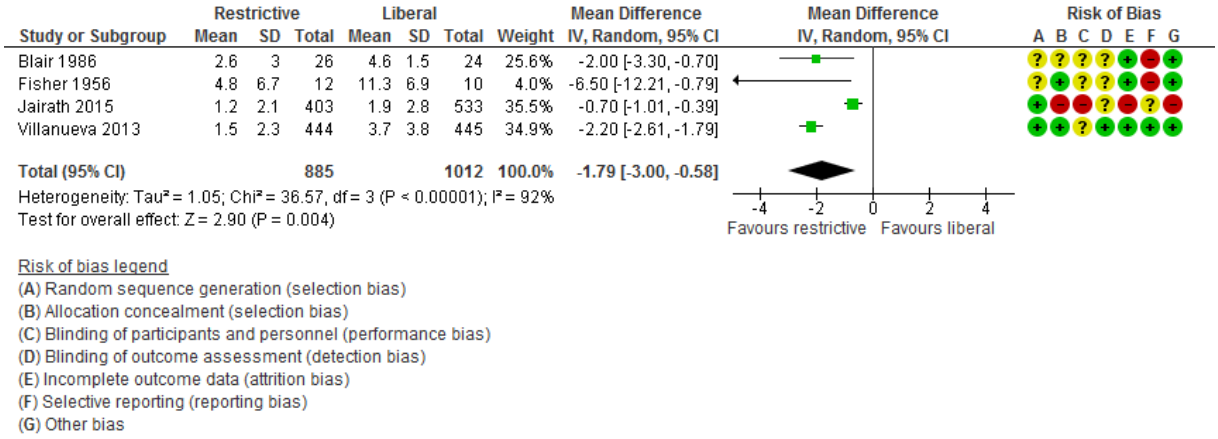


Figure 41: Forest plot of outcome: Units of blood transfused.

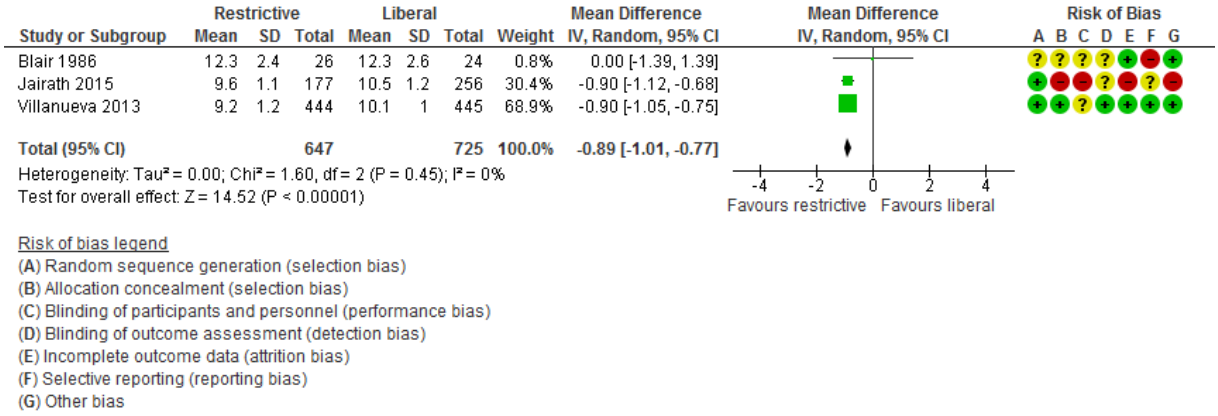


Figure 42: Forest plot of outcome: Haemoglobin concentration.

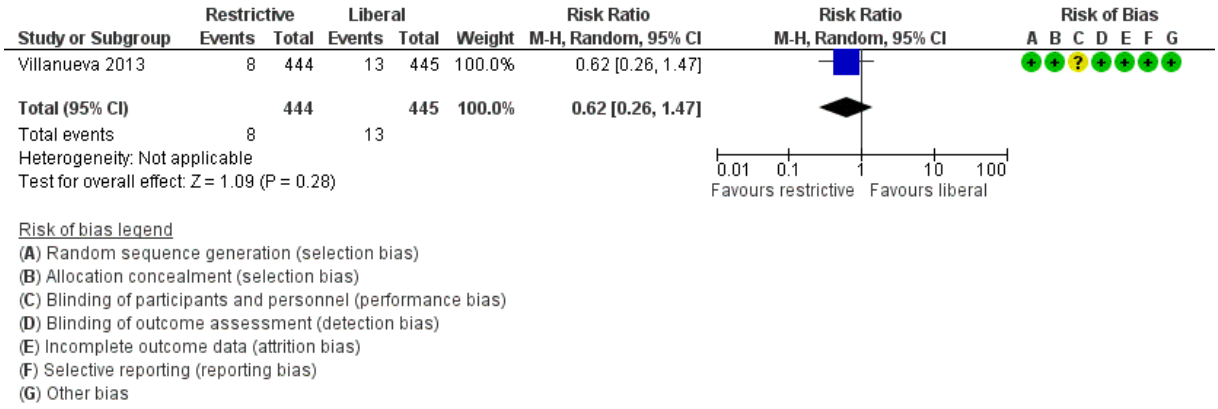


Figure 43: Forest plot outcome: Myocardial infarction.

Figure 44: Forest plot of outcome: Congestive heart failure.

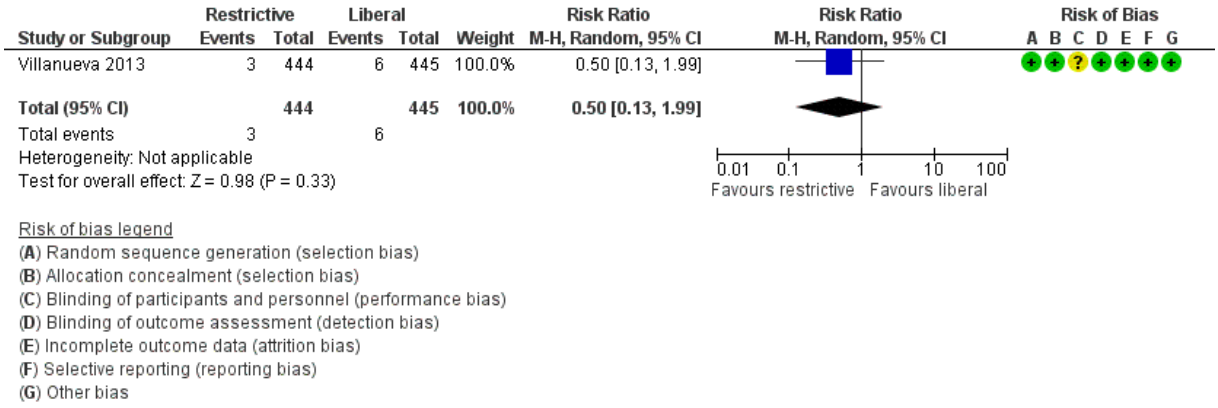


Figure 45: Forest plot of outcome: Cerebrovascular accident (CVA) - Stroke.

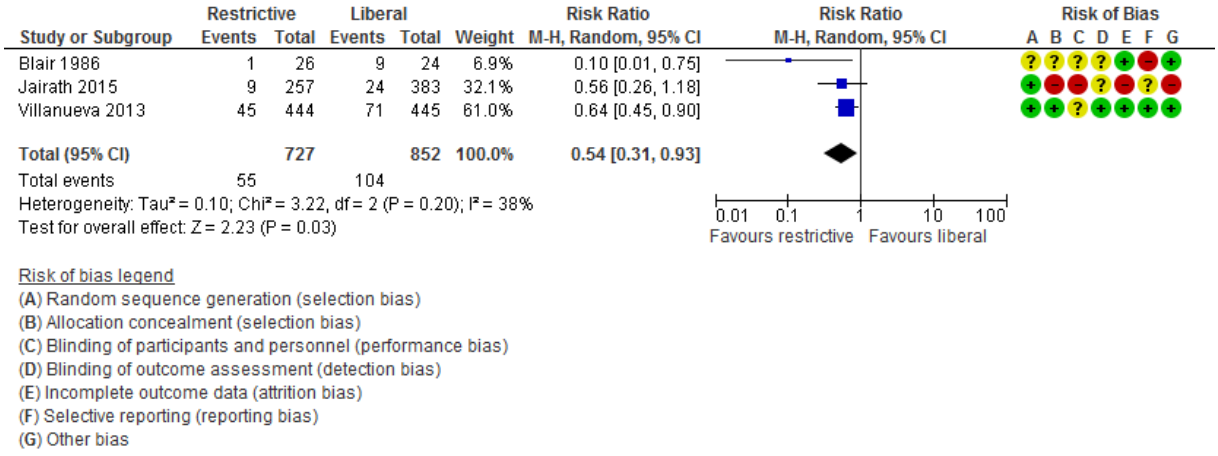


Figure 46: Forest plot of outcome: Rebleeding.

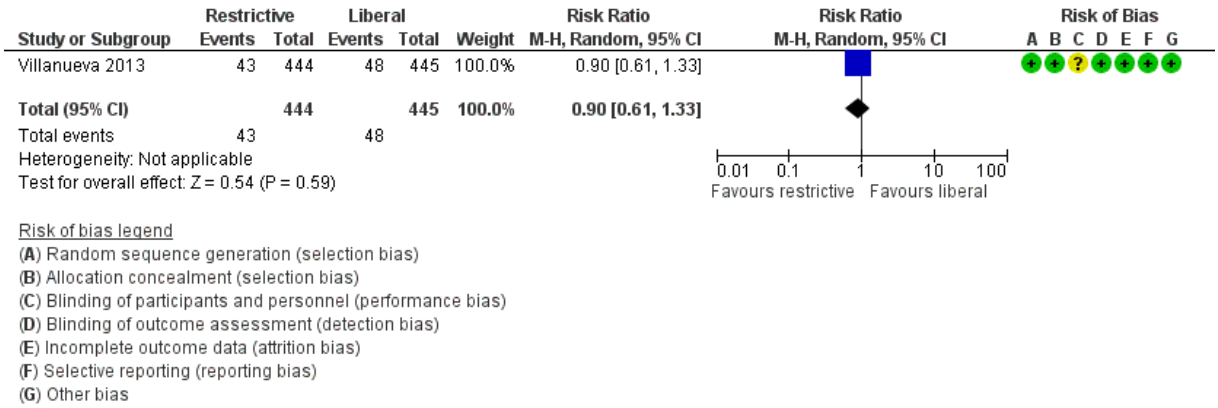


Figure 47: Forest plot of outcome: Pneumonia.

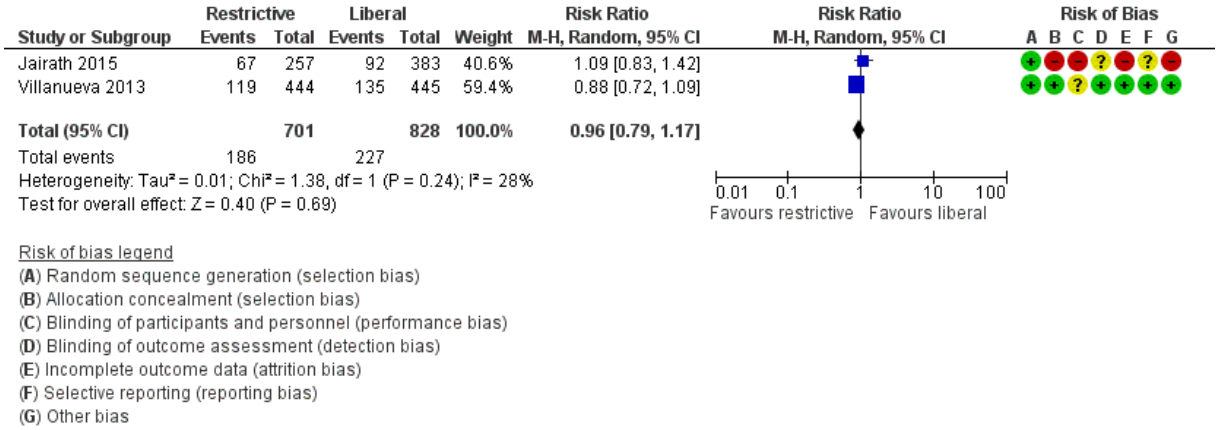


Figure 48: Forest plot of outcome: Pneumonia or wound infection.

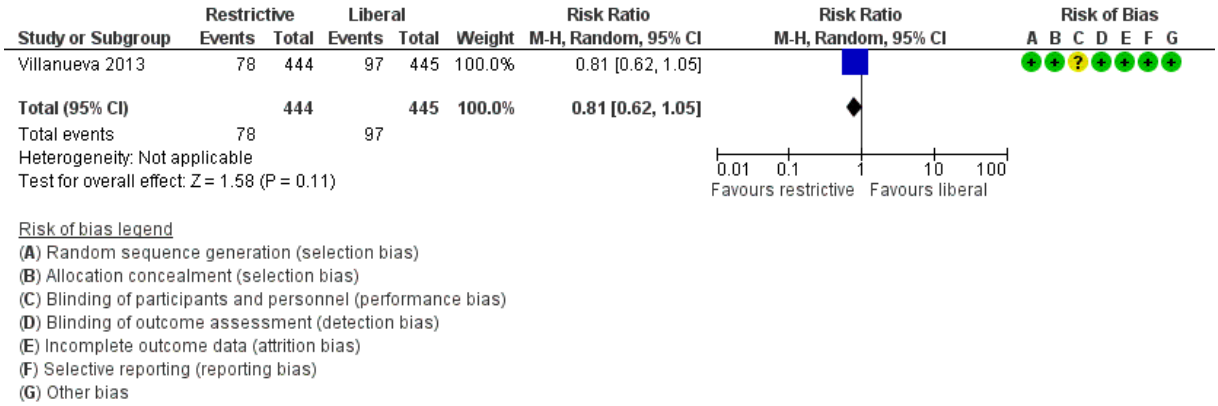


Figure 49: Forest plot of outcome: Renal failure.

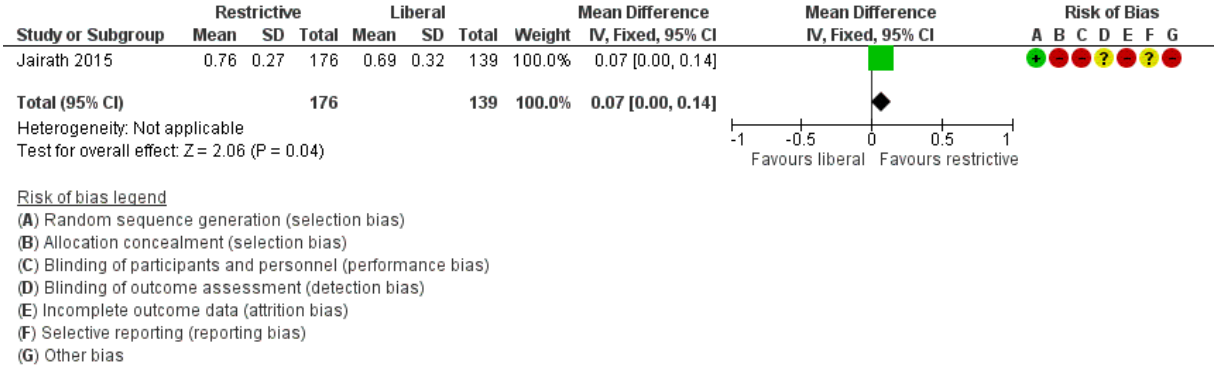


Figure 50: Forest plot of outcome: Function and fatigue - EuroQol (EQ-5D).

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Blair, 1986,	Randomization: Unclear, no information. Allocation concealment: Unclear, no information.	Participants and personnel: Unclear, no information. Outcome assessors: Unclear, no information.	No, no missing data.	No	No
Jairath, 2015,	Randomization: No, hospital was randomized, not the individual participant. Allocation concealment: Yes, hospital was randomized, so everyone knew which arm the participants were in.	Participants and personnel: Yes, trial was not blinded. Outcome assessors: Unclear, mortality allows low risk of bias but assessment of other clinical outcomes was unblended.	Yes, high percentage of missing data.	Unclear, no reporting bias was apparent.	Yes, differential enrolment by treatment arms.
Villanueva , 2013	Randomization: No, random sequence generation by computer. Allocation concealment: No, use of sealed consecutively numbered, opaque envelopes.	Participants and personnel: Unclear, clinicians and participants were not blinded. Outcome assessors: No, mortality was primary outcome. Assessors of other outcomes were not documented to be blinded.	No, good follow-up.	No, complete reporting.	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **Blair 1986** Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. *Effect of early blood transfusion on gastrointestinal haemorrhage.* Br J Surg 1986, 73(10):783–5. **Jairath 2015** Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, James MW, et al. *Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial.* Lancet 2015, 386(9989):137–44.

	Villanueva 2013 Colomo A, Hernandez-Gea V, Muniz-Diaz E, Madoz P, Aracil C, Alvarez-Urturi C. *Transfusion strategies in patients with cirrhosis and acute gastrointestinal bleeding.* Hepatology 2008, 48(4(Suppl)):413A. *Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. *Transfusion strategies for acute upper gastrointestinal bleeding.* N Engl J Med 2013, 368(1):11–21. **Systematic reviews** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease.* In peer-review [February 2018]. * Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 7: RBC transfusion triggers in adult patients with symptomatic/acute coronary heart disease

Overview evidence table GRADE software (PICO 7)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
30-day mortality												
2	randomised trials	not serious	not serious	not serious	very serious [a]	none	9/78 (11.5%)	0.0%	**RR 3.88** (0.83 to 18.13)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospital mortality												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/24 (8.3%)	1/21 (4.8%)	**RR 1.75** (0.17 to 17.95)	**36 more per 1.000** (from 40 fewer to 807 more)	⨁⨁◯◯ LOW	CRITICAL
Participants exposed to RBC transfusion												
2	randomised trials	not serious	not serious [b]	not serious	very serious [a]	none	28/79 (35.4%)	76/76 (100.0%)	**RR 0.40** (0.19 to 0.82)	**600 fewer per 1.000** (from 180 fewer to 810 fewer)	⨁⨁◯◯ LOW	IMPORTANT
RBC units transfused												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	24	21	-	MD **0.9 units lower** (1.87 lower to 0.07 higher)	⨁⨁◯◯ LOW	IMPORTANT
Haemoglobin concentration												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	55	55	-	MD **1.52 lower** (1.79 lower to 1.25 lower)	⨁⨁◯◯ LOW	IMPORTANT
Myocardial infarction												
2	randomised trials	not serious	not serious	not serious	very serious [a]	none	7/77 (9.1%)	6/74 (8.1%)	**RR 1.20** (0.43 to 3.34)	**16 more per 1.000** (from 46 fewer to 190 more)	⨁⨁◯◯ LOW	CRITICAL
Congestive heart failure												
2	randomised trials	not serious	serious [c]	not serious	very serious [a]	none	9/78 (11.5%)	10/76 (13.2%)	**RR 0.87** (0.06 to 13.46)	**17 fewer per 1.000** (from 124 fewer to 1.000 more)	⨁◯◯◯ VERY LOW	CRITICAL
CVA-stroke												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	0/54 (0.0%)	1/55 (1.8%)	**RR 0.34** (0.01 to 8.15)	**12 fewer per 1.000** (from 18 fewer to 130 more)	⨁⨁◯◯ LOW	CRITICAL
Sepsis-bacteraemia												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	0/54 (0.0%)	0/55 (0.0%)	not estimable		⨁⨁◯◯ LOW	IMPORTANT
Pneumonia												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/54 (3.7%)	0/55 (0.0%)	**RR 5.09** (0.25 to 103.64)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Pneumonia or wound infection												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/54 (3.7%)	0/55 (0.0%)	**RR 5.09** (0.25 to 103.64)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Thromboembolism												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <8 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	0/54 (0.0%)	1/55 (1.8%)	**RR 0.34** (0.01 to 8.15)	**12 fewer per 1.000** (from 18 fewer to 130 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Low number of events, limited sample size and/or large variability in results

b. Decision not to downgrade by reviewer(s) although point estimates vary, CIs show minimal overlap, test for heterogeneity shows a low p-value and I2>75%. This large inconsistency or variability is, however, not considered important as the direction of effect is the same for all studies which is most relevant for this outcome.

c. Decision to downgrade by reviewer(s) since point estimates vary, CIs show minimal overlap, test for heterogeneity shows a low p-value and I2>75%. Moreover, the point estimates point to different directions of effect.

Detailed evidence summary (PICO 7)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with symptomatic coronary heart disease (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. <u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6 **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 **Embase** (via Embase.com interface) using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 **Transfusion evidence library** (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: patients with symptomatic coronary heart disease. **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).

	Study design: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) (cluster) randomized controlled trials identified in the update. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes**.**

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Study funding, financial COI and remarks
Carson, 2013, USA	Randomised controlled trial	110 participants with acute myocardial infarction or undergoing cardiac catheterisation with Hb<10 g/dL (clinical specialty subgroup (Carson, 2016): acute myocardial infarction) Restrictive group: n=55, 27 males and 28 females, age=74.3±11.1 years Liberal group: n=55, 28 males and 27 females, age=67.3±13.6 years	Restrictive group (intervention): transfusion permitted if symptoms of anemia or Hb<8 g/dL; 1 unit at a time until symptoms disappeared or Hb increased >8 g/dL Liberal group (control): immediately transfuse 1 unit after randomisation (Hb<10 g/dL) and transfuse enough blood to maintain Hb>10 g/dL Transfusion: RBC units	Research supported by government grant from National Heart Lung and Blood Institute. Identified from the systematic review of Carson et al., 2016.
Cooper, 2011, USA	Randomised controlled trial	45 participants with acute myocardial infarction and haematocrit less than 30% (clinical specialty subgroup (Carson, 2016): acute myocardial infarction)	Restrictive group (intervention): transfusion with RBC if haematocrit <24%; target haematocrit: 24-27% (Hb: 8-9 g/dL) Liberal group (control):	Study was supported by the Cardiovascular Research Institute of the Washington

		Restrictive group: n=24, 13 males and 11 females, age=70.3±14.3 years Liberal group: n=21, 10 males and 11 females, age=76.4±13.5 years	transfusion with RBC if haematocrit <30%; target haematocrit: 30-33% (Hb: 10-11 g/dL) Transfusion: Leukocyte-depleted packed RBC	Hospital Center. Identified from the systematic review of Carson et al., 2016.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcomes				
30-day mortality	Restrictive vs liberal transfusion threshold	Not statistically significant: 9/78 vs 2/76 § RR: 3.88, 95%CI [0.83;18.13] ¥ (p=0.085) (Figure 51)	2, 78 vs 76	Carson, 2013; Cooper, 2011
Hospital mortality		Not statistically significant: 2/24 vs 1/21 § RR: 1.75, 95%CI [0.17;17.95] ¥ (p=0.64)* (Figure 52)	1, 24 vs 21	Cooper, 2011
Participants exposed to blood transfusion		Statistically significant: 28/79 vs 76/76 § RR: 0.40, 95%CI [0.19;0.82] (p=0.012) (Figure 53) *In favour of restrictive transfusion threshold*	2, 79 vs 76	Carson, 2013; Cooper, 2011
Units of blood transfused		Not statistically significant: 1.6±2.0 vs 2.5±1.3 MD: -0.90, 95%CI [-1.87;0.07] ¥ (p=0.07)* (Figure 54)	1, 24 vs 21 §	Cooper, 2011
Secondary outcomes				
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	Statistically significant: 9.12±0.75 vs 10.64±0.71 MD: -1.52, 95%CI [-1.79;-1.25] (p<0.00001)* (Figure 55)	1, 55 vs 55 §	Carson, 2013
Myocardial infarction		Not statistically significant: 7/77 vs 6/74 § RR: 1.20, 95%CI [0.43;3.34] ¥ (p=0.73)** (Figure 56)	2, 77 vs 74	Carson, 2013; Cooper, 2011
Congestive heart failure		Not statistically significant: 9/78 vs 10/76 § RR: 0.87, 95%CI [0.06;13.46] ¥ (p=0.92)** (Figure 57)	2, 78 vs 76	
Cerebrovascular accident (CVA) - Stroke		Not statistically significant: 0/54 vs 1/55 § RR: 0.34, 95%CI [0.01; 8.15] ¥ (p=0.51)* (Figure 58)	1, 54 vs 55	Carson, 2013
Sepsis/bacteraemia		0/54 vs 0/55 § RR: not estimable (Figure 59)		

Pneumonia		Not statistically significant: 2/54 vs 0/55 § RR: 5.09, 95%CI [0.25;103.64] ¥ (p=0.29)* (Figure 60)		
Pneumonia or wound infection		Not statistically significant: 2/54 vs 0/55 § RR: 5.09, 95%CI [0.25;103.64] ¥ (p=0.29)* (Figure 61)		
Thromboembolism		Not statistically significant: 0/54 vs 1/55 § RR: 0.34, 95%CI [0.01; 8.15] ¥ (p=0.51)* (Figure 62)		

Mean ± SD (unless otherwise indicated)

* Calculations (p-value) done by the reviewer(s) using Review Manager software

** Calculations (RR, 95%CI and p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

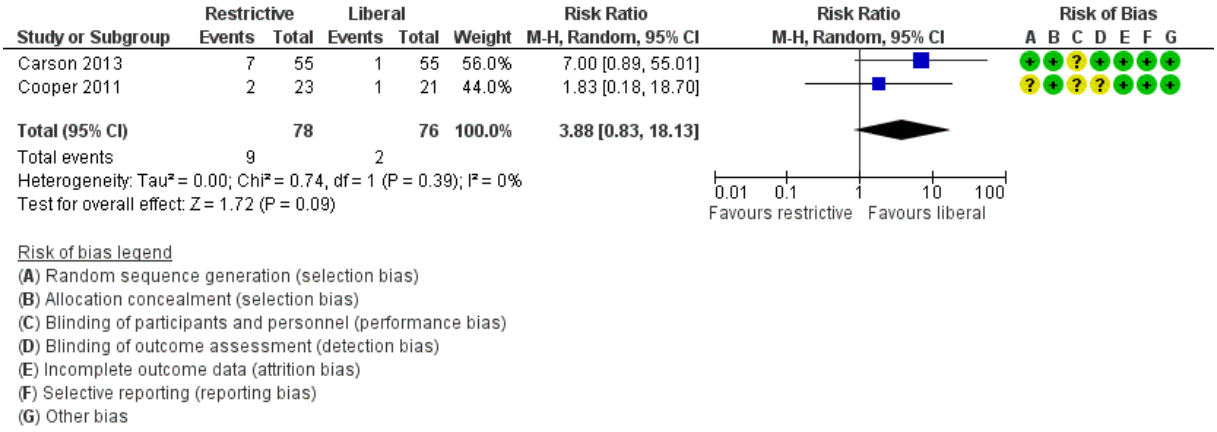


Figure 51: Forest plot of outcome: 30-day mortality.

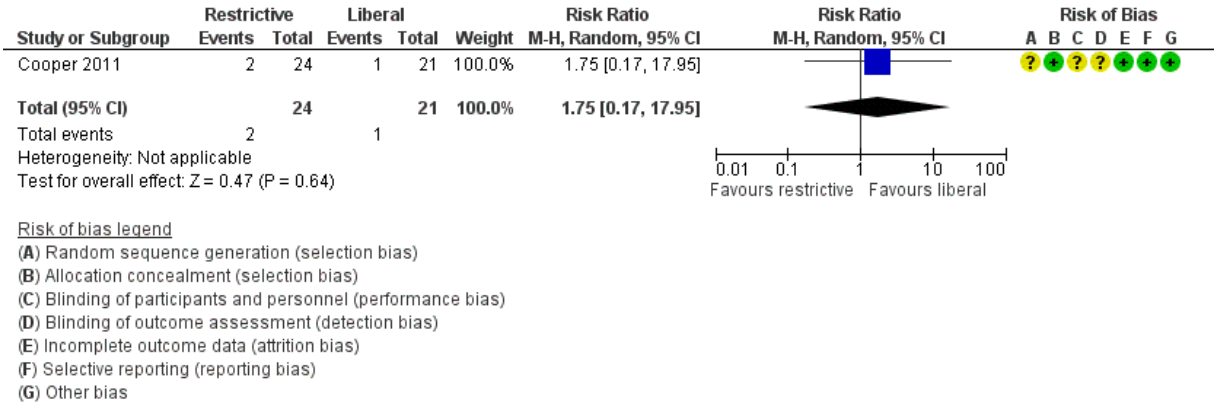


Figure 52: Forest plot of outcome: Hospital mortality.

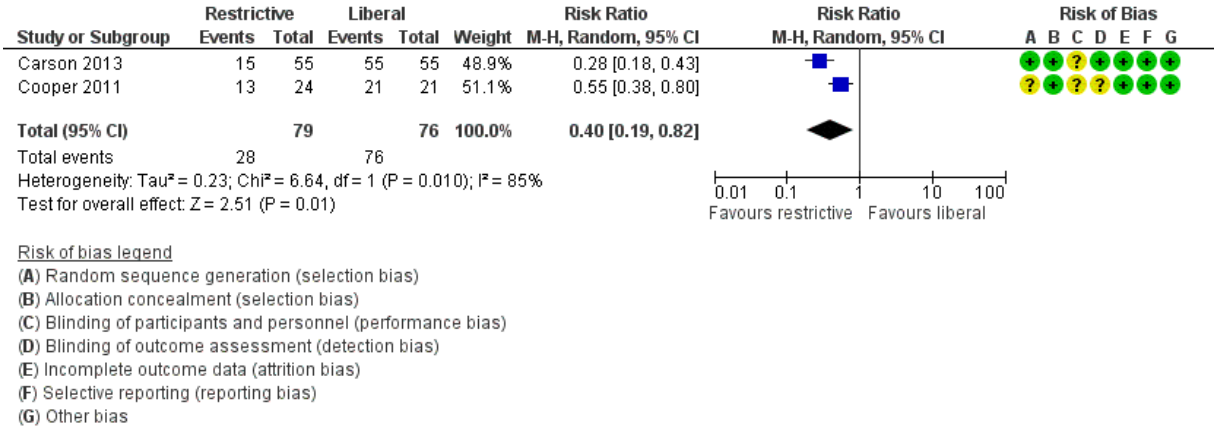
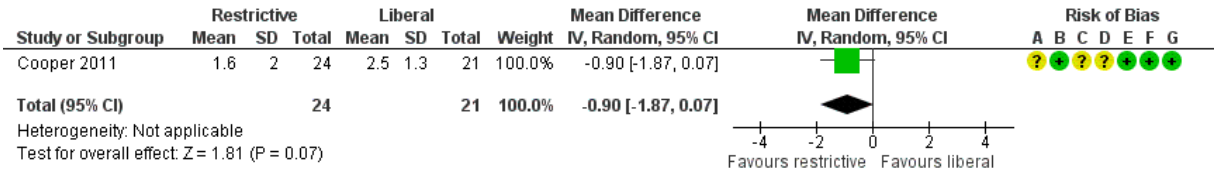
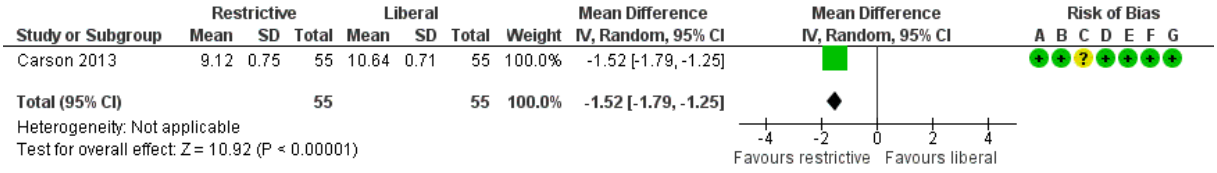


Figure 53: Forest plot of outcome: Participants exposed to blood transfusion.



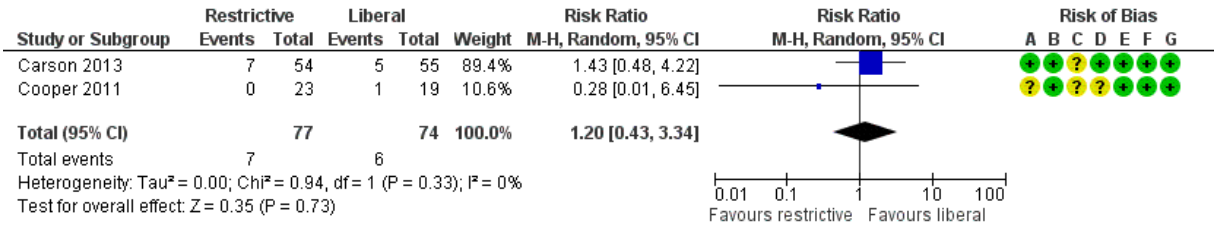
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 54: Forest plot of outcome: Units of blood transfused.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 55: Forest plot of outcome: Haemoglobin concentration.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 56: Forest plot of outcome: Myocardial infarction.

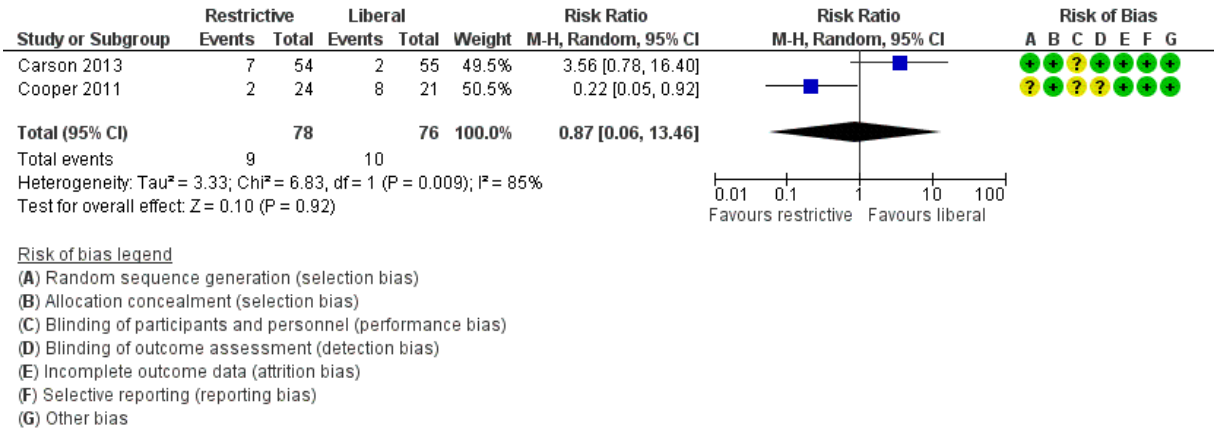


Figure 57: Forest plot of outcome: Congestive heart failure.

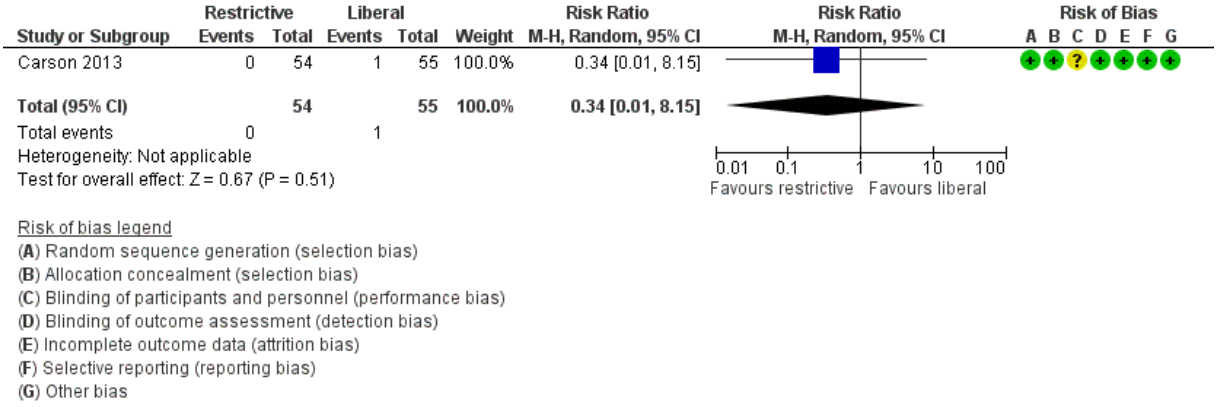


Figure 58: Forest plot of outcome: Cerebrovascular (CVA) - stroke.

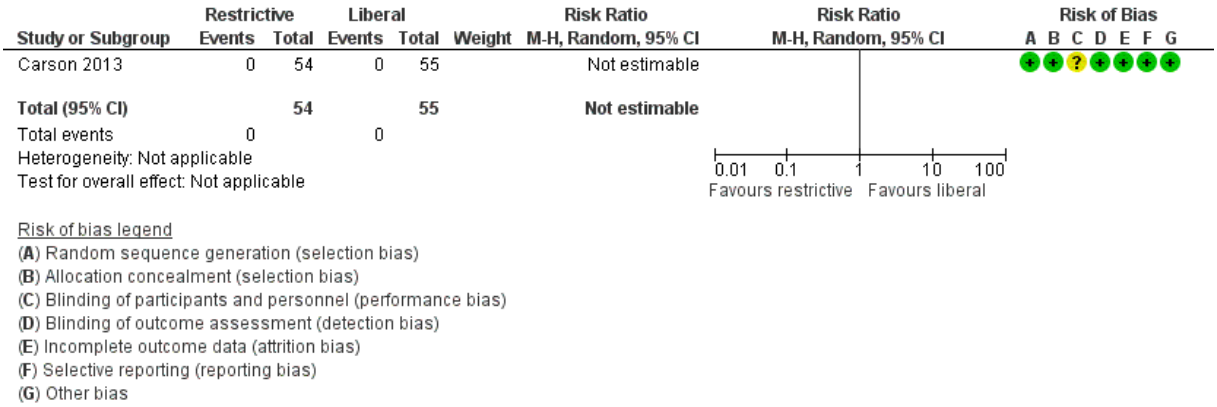
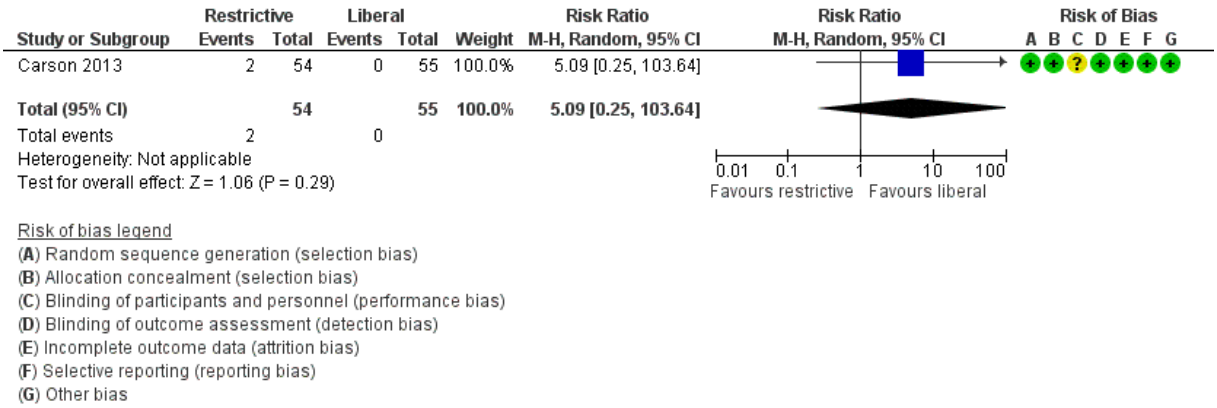
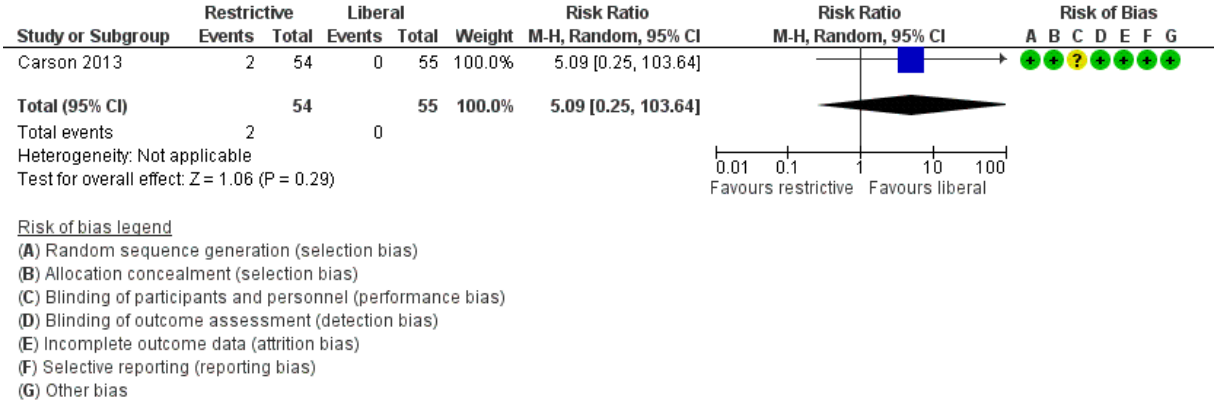


Figure 59: Forest plot of outcome: Sepsis/bacteraemia.



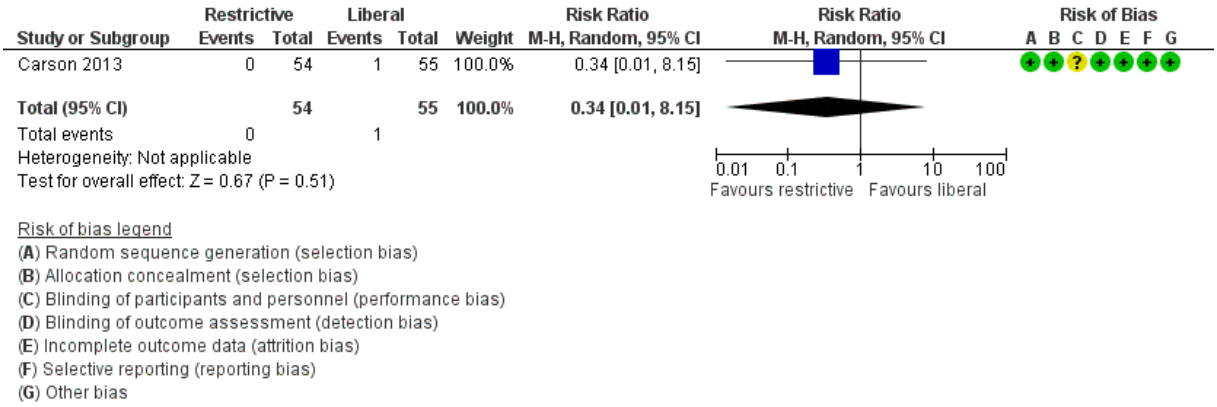
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 60: Forest plot of outcome: Pneumonia.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 61: Forest plot of outcome: Pneumonia or wound infection.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 62: Forest plot of outcome: Thromboembolism.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Carson, 2013, USA	Randomization: No, computer programme generated allocation sequence Allocation concealment: No, central telephone randomization	Participants and personnel: Unclear, not blinded but unlikely to affect outcome Outcome assessors: No, all primary and most secondary outcomes assessed blindly	No, only 1 of 110 participants lost to follow-up	No Pre-registration of study protocol (NCT01167582)	No
Cooper, 2011, USA	Randomization: Unclear, no information provided Allocation concealment: No, use of consecutively numbered opaque envelopes	Participants and personnel: Unclear, not blinded Outcome assessors: Unclear, local investigator determined outcomes	No, complete in-hospital follow-up. 3 of 45 participants lost to follow-up at 30 days.	No Pre-registration of study protocol (NCT00126334)	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, et al. *Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease.* Am Heart J 2013;165(6):964–71. Cooper HA, Rao SV, Greenberg MD, Rumsey MP, Mckenzie M, Alcorn KW, et al. *Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT randomized pilot study).* Am J Cardiol 2011;108(8):1108–11. **Systematic reviews** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease.* In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 8: RBC transfusion triggers in adult patients with septic shock

Overview evidence table GRADE software (PICO 8)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <9 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
28-30-day mortality												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	252/653 (38.6%)	242/645 (37.5%)	**RR 1.07** (0.83 to 1.39)	**26 more per 1.000** (from 64 fewer to 146 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital mortality												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	151/502 (30.1%)	154/496 (31.0%)	**RR 0.97** (0.80 to 1.17)	**9 fewer per 1.000** (from 53 more to 62 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
90-day mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <9 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	serious [a]	none	322/653 (49.3%)	311/645 (48.2%)	**RR 1.06** (0.85 to 1.32)	**29 more per 1.000** (from 72 fewer to 154 more)	⊕⊕⊕◯ MODERATE	CRITICAL
1-year mortality												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	268/501 (53.5%)	271/496 (54.6%)	**RR 0.98** (0.87 to 1.10)	**11 fewer per 1.000** (from 55 more to 71 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Mortality at the time of longest follow-up												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	284/501 (56.7%)	302/495 (61.0%)	**RR 0.93** (0.84 to 1.03)	**43 fewer per 1.000** (from 18 more to 98 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Patients exposed to RBC transfusion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <9 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	not serious	none	388/653 (59.4%)	581/645 (90.1%)	**RR 0.66** (0.62 to 0.70)	**306 fewer per 1.000** (from 270 fewer to 342 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Haemoglobin concentration												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	502	496	-	MD **1.7 lower** (1.82 lower to 1.58 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Myocardial infarction												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	46/639 (7.2%)	30/638 (4.7%)	**RR 1.49** (0.97 to 2.28)	**23 more per 1.000** (from 1 fewer to 60 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Congestive heart failure												
1	randomised trials	not serious	not serious	serious [b]	serious [c]	none	0/488 (0.0%)	0/489 (0.0%)	not estimable		⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <9 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
CVA-stroke												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	7/639 (1.1%)	12/638 (1.9%)	**RR 0.64** (0.19 to 2.20)	**7 fewer per 1.000** (from 15 fewer to 23 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Rebleeding												
1	randomised trials	not serious	not serious	serious [b]	not serious	none	147/488 (30.1%)	148/489 (30.3%)	**RR 1.00** (0.82 to 1.20)	**0 fewer per 1.000** (from 54 fewer to 61 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Renal failure												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	127/583 (21.8%)	101/578 (17.5%)	**RR 1.25** (0.99 to 1.57)	**44 more per 1.000** (from 2 fewer to 100 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Danish short form health survey questionnaire (SF-36): physical component summary score												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <9 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [b]	serious [a]	none	311	318	-	MD **0.4 points higher** (4.05 lower to 4.85 higher)	⨁⨁◯◯ LOW	IMPORTANT
Danish short form health survey questionnaire (SF-36): mental component summary score												
1	randomised trials	not serious	not serious	serious [b]	serious [a]	none	311	318	-	MD **0.5 points higher** (5.26 lower to 6.26 higher)	⨁⨁◯◯ LOW	IMPORTANT
60-day mortality												
1	randomised trials	not serious	not serious	serious [d]	serious [a]	none	99/151 (65.6%)	84/149 (56.4%)	**RR 1.16** (0.97 to 1.40)	**90 more per 1.000** (from 17 fewer to 226 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; a. Large variability in results; b. Lack of generalizibility: evidence from 1 study conducted in Denmark; c. Low number of events; d. Lack of generalizibility: evidence from 1 study conducted in Brazil

Detailed evidence summary (PICO 8)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with septic shock (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. <u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6 **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI]))

	#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 **Embase** (via Embase.com interface) using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 **Transfusion evidence library** (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: patients with septic shock in different settings (e.g. intensive care unit). **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** Primary: Mortality (e.g. 30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and Secondary: morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction,

	congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** Systematic reviews (+ meta-analyses) of experimental studies (RCT's). If not available, we will search for individual experimental studies (RCT's). To examine the evidence for the effect of transfusion threshold on the use of red blood cell (RBC) transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (with or without a specified level of haemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes relevant to this review.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Bergamin, 2017, Brazil	Experimental: RCT	300 adult cancer patients with septic shock in the first 6 hours of ICU admission. Restrictive group: n = 151, 84 males and 67 females, age=61.4±13.5 years Liberal group: n = 149, 70 males and 79 females, age=61.6±12.9 years	Restrictive group (intervention): RBC transfusion (1 unit) if Hb <7 g/dL Liberal group: RBC transfusion (1 unit) if Hb <9 g/dL HB levels assessed after IC admission, twice a day during ICU stay and after evry transfusion. Transfusion: leukodepleted RBC units	Dr. Park disclosed government work. The remaining authors have disclosed that they do not have any potential conflicts of interest. Identified from the update.
Holst, 2014, Denmark	Randomised controlled trial	998 participants in Denmark, Sweden, Norway and Finland with septic shock in the ICU and haemoglobin concentration less than 9 g/dL (clinical specialty subgroup (Carson, 2016): critical care)	Restrictive group (intervention): transfusion if Hb conc ≤7.0 g/dL Liberal group (control): transfusion if Hb ≤9.0 g/dL Haemoglobin concentrations were	Research funded by hospitals, medical societies and foundations. Two authors received grant support from private industry. Identified from the systematic review

		Restrictive group: n=502, 272 males and 230 females, median age (IQR)=67 (57-73) yrs Liberal group: n=496, 259 males and 237 females, median age (IQR)=67 (58-75) yrs	reassessed within 3 hours after termination of the transfusion or before the initiation of another transfusion. Transfusion: single units of cross-matched, prestorage leukoreduced red cells	of Carson et al., 2016. Two articles (one subgroup analysis and one follow-up) identified through the updated search: Rygård 2016 (follow-up) and Rygård 2017 (subgroup analysis). Relevant additional data from Rygård 2016 was extracted and included in the synthesis of findings.

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
Primary outcomes				
28-30 - day mortality	Restrictive vs liberal transfusion threshold	Not statistically significant: 252/653 vs 242/645 RR: 1.07, 95%CI [0.83;1.39] ¥ (p=0.60)* (Figure 63)	2, 653 vs 645	Bergamin 2017, Holst 2014
Hospital mortality		Not statistically significant: 151/502 vs 154/496 RR: 0.97, 95%CI [0.80;1.17] (p=0.74)* (Figure 64)	1, 502 vs 496	Holst 2014
60-day mortality		Not statistically significant: 99/151 vs 84/149 RR: 1.16, 95%CI [0.97;1.40] ¥ (p=0.10)* (Figure 65)	1, 151 vs 149	Bergamin 2017
90-day mortality		Not statistically significant: 322/653 vs 311/645 RR: 1.06, 95%CI [0.85;1.32] ¥ (p=0.59)* (Figure 66)	2, 653 vs 645	Bergamin 2017, Holst 2014
1-year mortality		Not statistically significant: 268/501 vs 271/496 RR: 0.98, 95%CI [0.87;1.10] (p=0.72)* (Figure 67)	1, 501 vs 496 (data from Rygård 2016 identified in search update)	Holst 2014
Mortality at the time of longest follow-up		Not statistically significant: 284/501 vs 302/495 RR: 0.93, 95%CI [0.84;1.03] (p=0.17)* (Figure 68)	1, 501 vs 495 (data from Rygård 2016 identified in search update)	
Participants exposed to blood transfusions		Statistically significant: 388/653 vs 581/645 RR: 0.66, 95%CI [0.62;0.70] (p<0.00001)* (Figure 69)	1, 653 vs 645	Bergamin 2017, Holst 2014

		In favour of restrictive transfusion threshold		
Units of blood transfused		Statistically significant: Median (IQR): 0 (0-2) vs 1 (0-3) Median difference: 1 (p<0.001) *In favour of restrictive transfusion threshold*	1, 151 vs 149	Bergamin 2017
		Statistically significant: Median (IQR): 1 (0-3) vs 4 (2-7) Median difference: 3 (p<0.001) *In favour of restrictive transfusion threshold*	1, 502 vs 496	Holst 2014
Secondary outcomes				
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	Statistically significant: 7.6±1.0 vs 9.3±0.9 MD: -1.70, 95%CI [-1.82;-1.58] (p<0.00001)* (Figure 70)	1, 502 vs 496	Holst 2014
Myocardial infarction		Not statistically significant: 46/639 vs 30/638 RR: 1.49, 95%CI [0.97;2.28] ¥ (p=0.07)* (Figure 71)	2, 639 vs 638	Bergamin 2017, Holst 2014
Congestive heart failure		0/488 vs 0/489 § RR: not estimable (Figure 72)	1, 488 vs 489	Holst 2014
Cerebrovascular accident (CVA) - Stroke		Not statistically significant: 7/639 vs 12/638 RR: 0.64, 95%CI [0.19;2.20] ¥ (p=0.48)* (Figure 73)	2, 639 vs 638	Bergamin 2017, Holst 2014
Rebleeding		Not statistically significant: 147/488 vs 148/489 RR: 1.00, 95%CI [0.82;1.20] (p=0.96)* (Figure 74)	1, 488 vs 489	Holst 2014
Renal failure		Not statistically significant: 127/583 vs 101/578 RR: 1.25, 95%CI [0.99;1.57] ¥ (p=0.06)* (Figure 75)	2, 583 vs 578	Bergamin 2017, Holst 2014
Danish short form health survey questionnaire (SF-36): physical component summary score		Not statistically significant: 7.6±27.8 vs 7.2±29.2 MD: 0.40, 95%CI [-4.05;4.85] ¥ (p=0.86)* (Figure 76)	1, 311 vs 318 (data from Rygård 2016 identified in search update)	Holst 2014
Danish short form health survey questionnaire (SF-36): mental component summary score		Not statistically significant: 10±36 vs 9.5±37.7 MD: 0.50, 95%CI [-5.26;6.26] ¥ (p=0.86)* (Figure 77)		

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference

* Calculations (RR or MD, 95% CI and/or p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

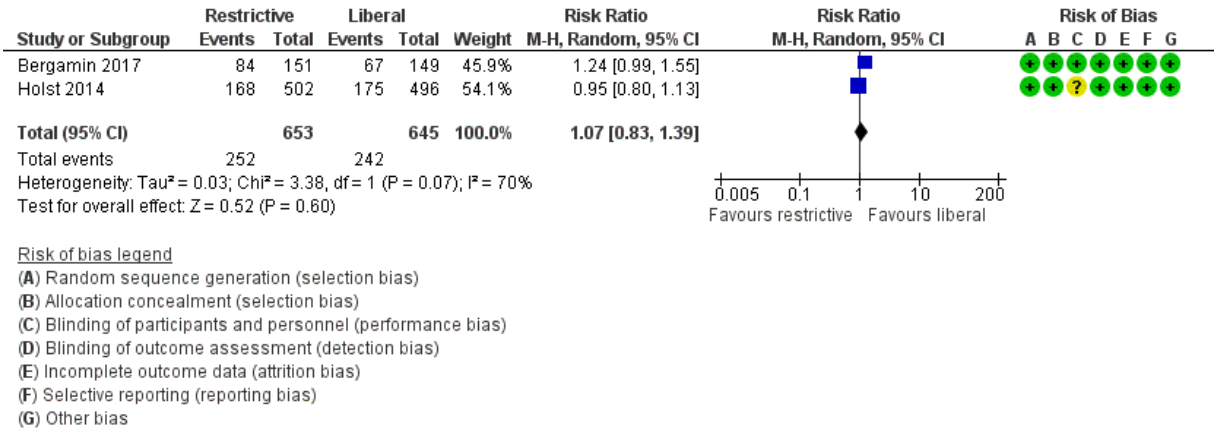


Figure 63: Forest plot of outcome: 28-30 - day mortality.

Figure 64: Forest plot of outcome: Hospital mortality.

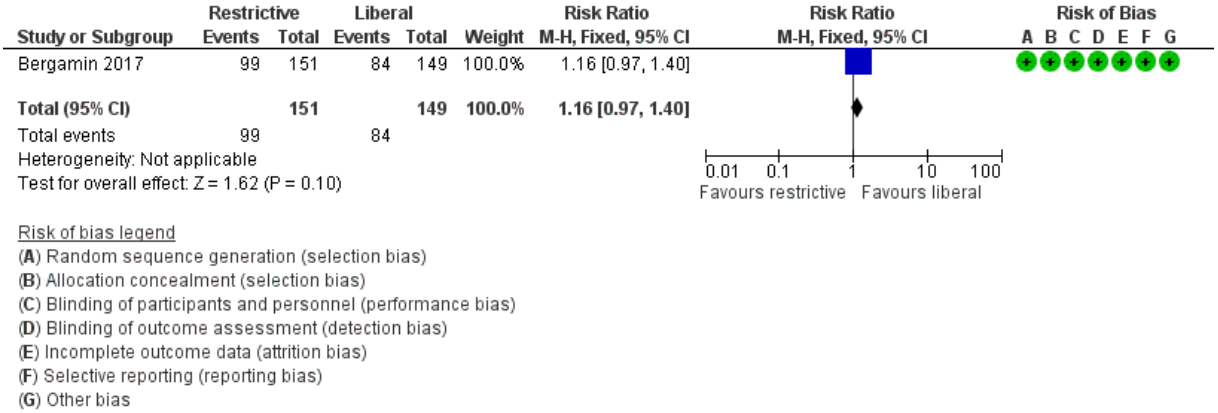


Figure 65: Forest plot of outcome: 60-day mortality.

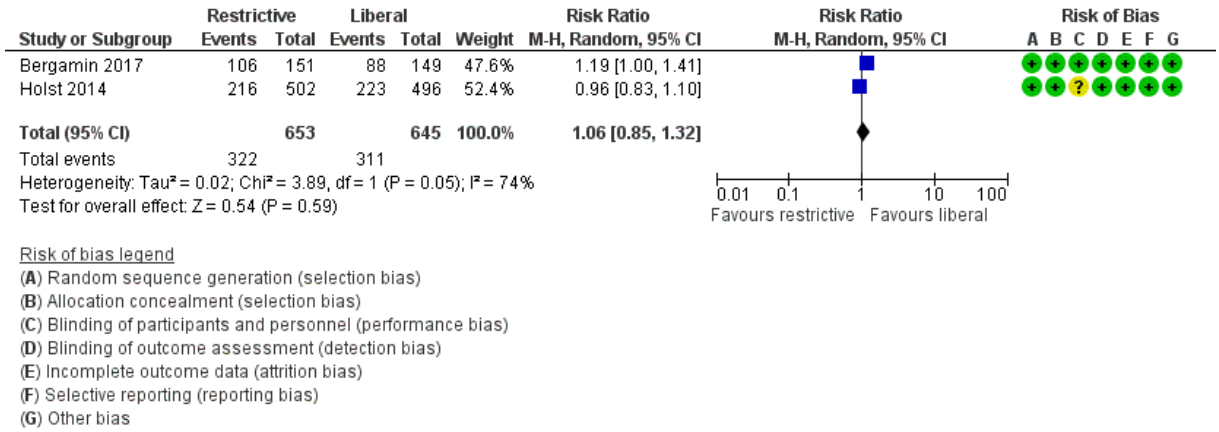


Figure 66: Forest plot of outcome: 90-day mortality.

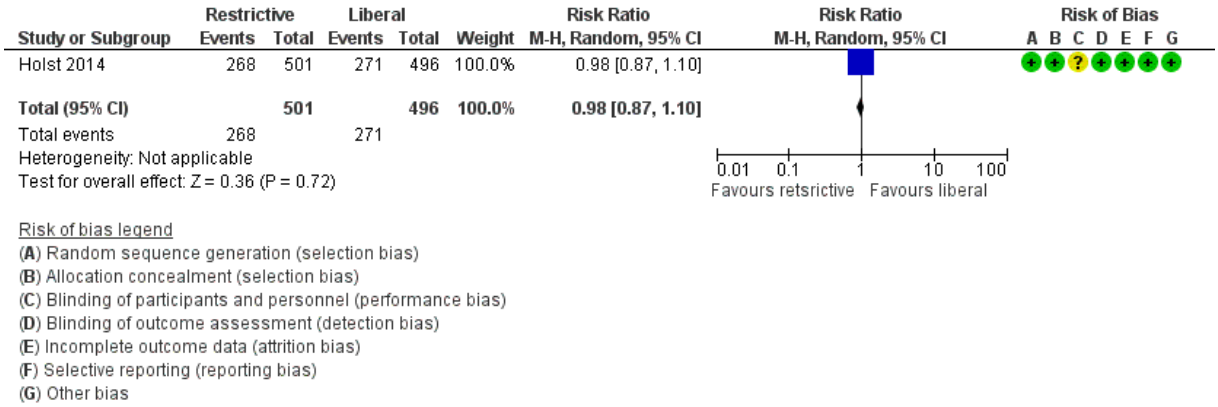


Figure 67: Forest plot of outcome: 1-year mortality

Figure 68: Forest plot of outcome: Mortality at the time of longest follow-up

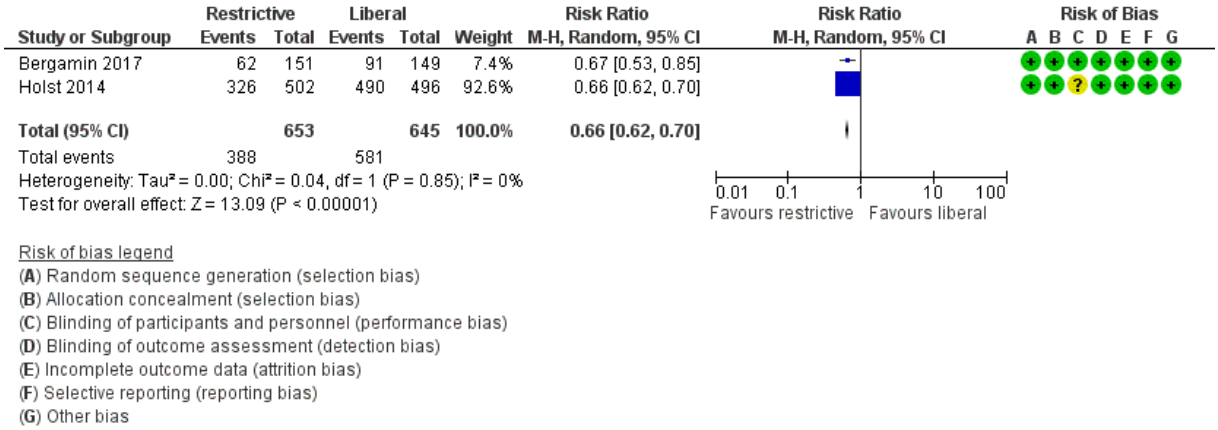


Figure 69: Forest plot of outcome: Participants exposed to blood transfusions.

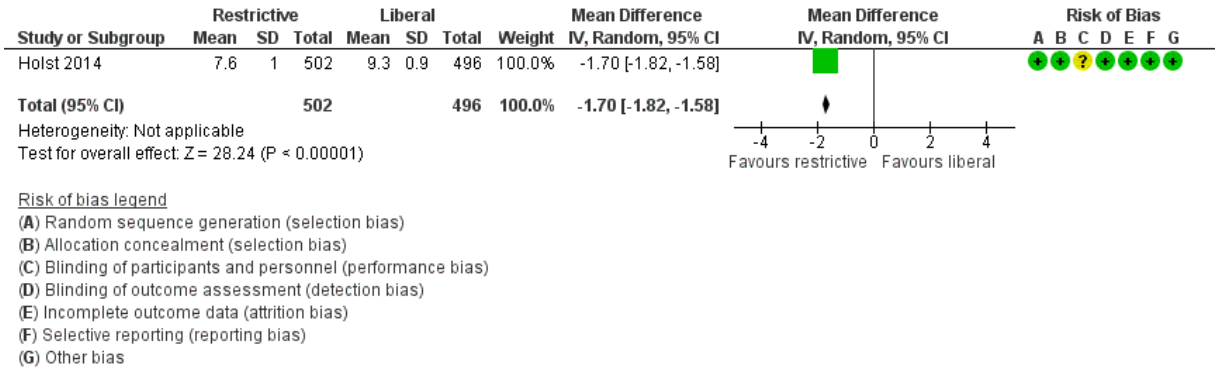


Figure 70: Forest plot of outcome: Haemoglobin concentration.

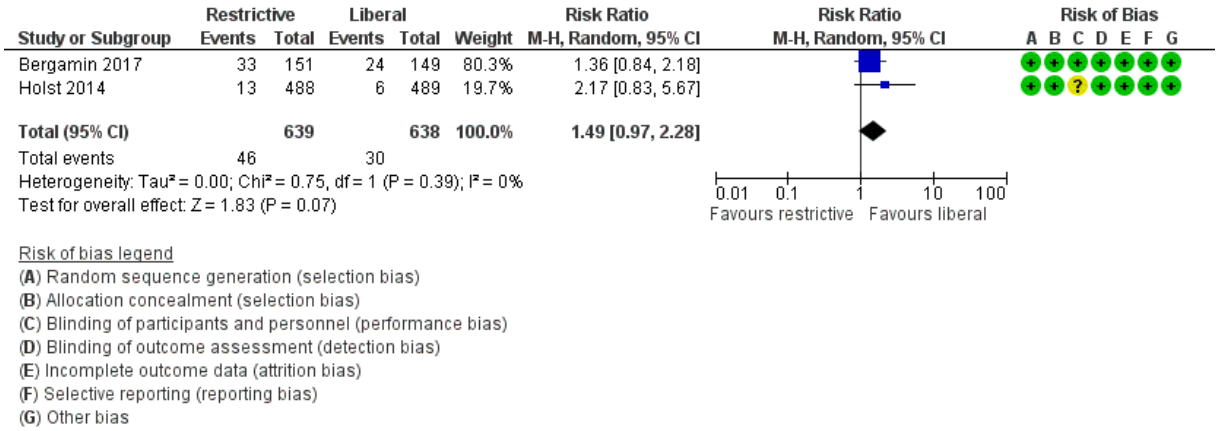


Figure 71: Forest plot of outcome: Myocardial infarction.

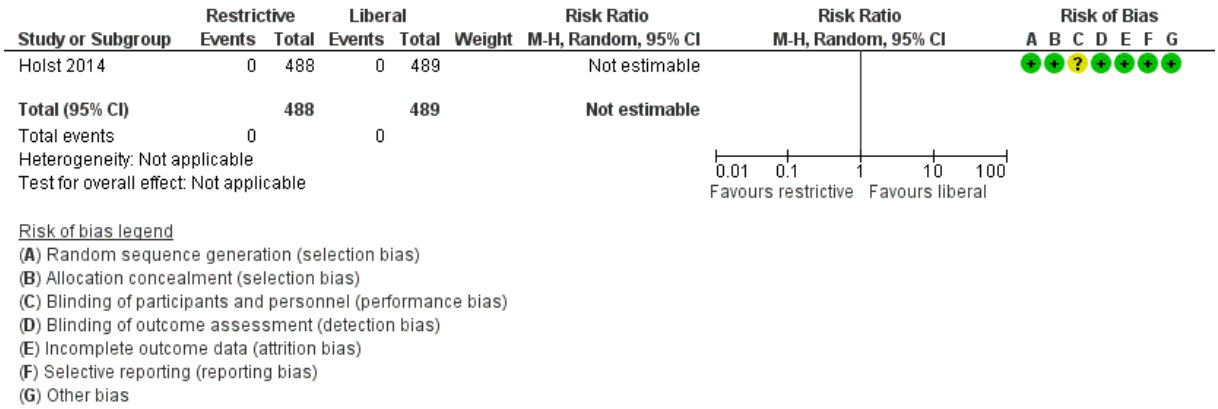


Figure 72: Forest plot of outcome: Congestive heart failure.

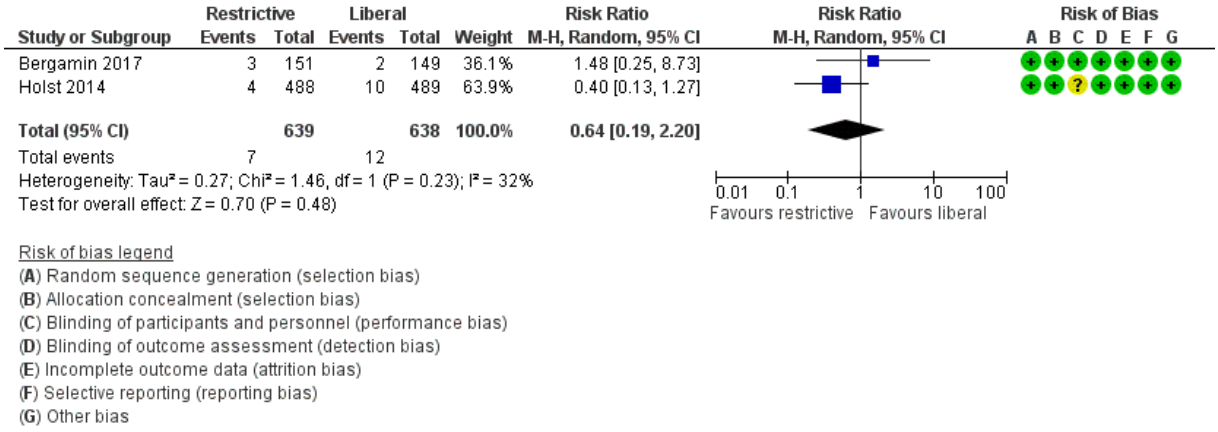


Figure 73: Forest plot of outcome: Cerebrovascular accident (CVA) - Stroke.

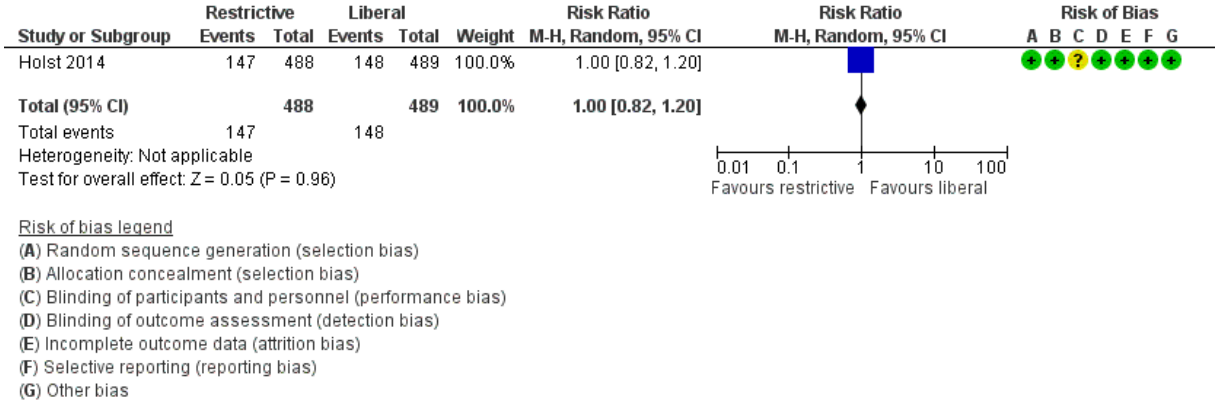


Figure 74: Forest plot of outcome: Rebleeding.

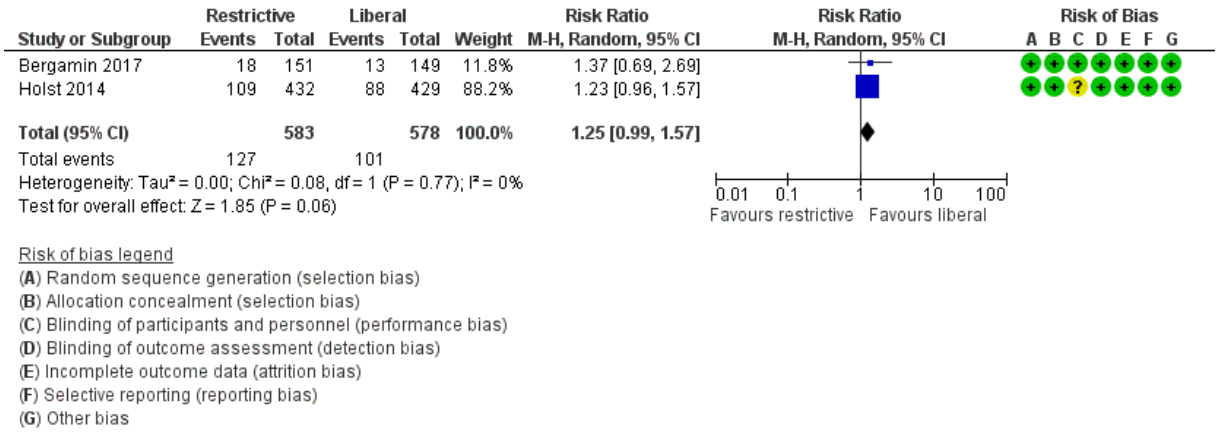


Figure 75: Forest plot of outcome: Renal failure.

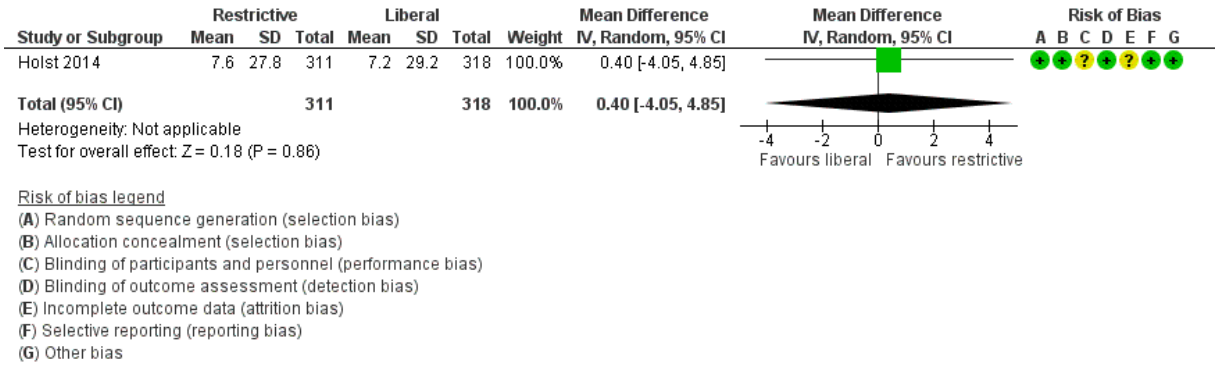


Figure 76: Forest plot of outcome: Danish short form health survey questionnaire (SF-36): physical component summary score

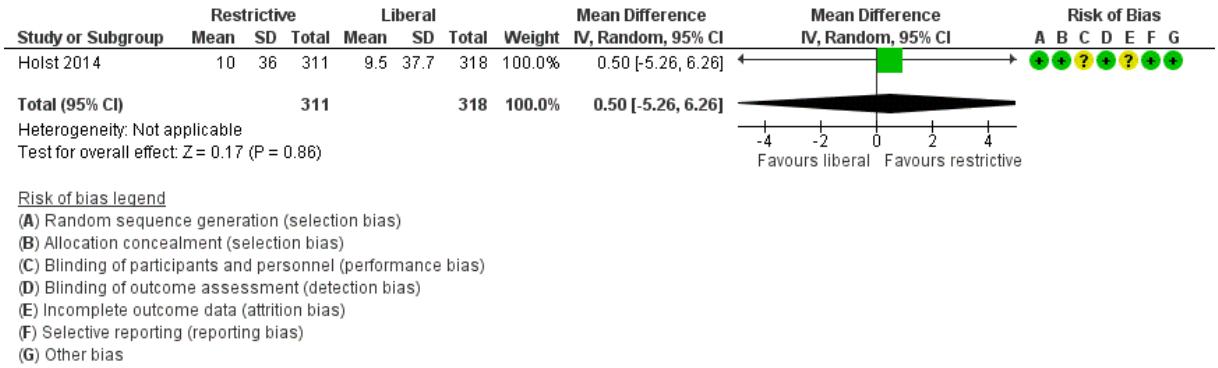


Figure 77: Forest plot of outcome: Danish short form health survey questionnaire (SF-36): mental component summary score

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Bergamin, 2017	Randomization: no, an internet-based system was used Allocation concealment: no internet-based system concealed assignments	Personnel and participants: no, physicians and nurses of the ICU were aware, patients and investigators were blinded Outcome assessment: no, 2 blinded investigators assessed outcomes	No, no exclusions after randomization or loss to follow-up	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT01648946)	No
Holst, 2014	Randomization: No, a centralised computer generated the assignment sequence. Allocation concealment: No, use of a centralised computer ensured allocation concealment.	Participants and personnel: Unclear, clinicians were not blinded. Outcome assessors: No, the investigators assessing mortality (the DSMB) and the trial statistician were blinded.	main study (Holst 2014): No, near complete follow-up. follow-up study (Rygård 2016 identified in search update): Unclear, considerable loss to follow-up for health survey questionnaire. Responders are older and suffered more often had a pulmonary source of sepsis. Among responders, baseline characteristics were similar in the two intervention groups.	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT01485315)	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **Bergamin 2017** Bergamin FS, Almeida JP, Landoni G, Galas FRBG, Fukushima JT, Fominskiy E, Park CHL, Osawa EA, Diz MPE, Oliveira GQ, Franco RA, Nakamura RE, Almeida EM, Abdala E, Freire MP, Filho RK, Auler JOC Jr, Hajjar LA. *Liberal Versus Restrictive*

	Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. Crit Care Med. 2017, 45(5):766-773. Identified in search update. **Holst 2014** *Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. TRISS Trial Group. Scandinavian Critical Care Trials Group. *Lower versus higher hemoglobin threshold for transfusion in septic shock.* N Engl J Med 2014, 371(15):1381-91. Rygård SL, Holst LB, Wetterslev J, Winkel P, Johansson PI, Wernerman J, et al. TRISS Trial Group. Scandinavian Critical Care Trials Group. *Long-term outcomes in patients with septic shock transfused at a lower versus a higher haemoglobin threshold: the TRISS randomised, multicentre clinical trial.* Intensive Care Med 2016, 42(11):1685-1694. Identified in search update. Rygård SL, Holst LB, Wetterslev J, Johansson PI, Perner A. TRISS trial group. Scandinavian Critical Care Trials Group. *Higher vs. lower haemoglobin threshold for transfusion in septic shock: subgroup analyses of the TRISS trial.* Acta Anaesthesiol Scand 2017, 61(2):166-175. Identified in search update. **<u>Systematic reviews</u>** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease.* In peer-review [February 2018]. *Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 9: RBC transfusion triggers in adult cardiac surgery patients

Overview evidence table GRADE software (PICO 9)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
30-day mortality												
3	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	44/1464 (3.0%)	38/1478 (2.6%)	**RR 1.18** (0.77 to 1.81)	**5 more per 1.000** (from 6 fewer to 21 more)	⨁⨁⨁◯ MODERATE	CRITICAL
30-day mortality (subgroup: patients <60 years)												
1	randomised trials	not serious	not serious	serious [c]	serious [d]	none	5/124 (4.0%)	5/118 (4.2%)	**RR 0.95** (0.28 to 3.20)	**2 fewer per 1.000** (from 31 fewer to 93 more)	⨁⨁◯◯ LOW	CRITICAL
30-day mortality (subgroup: patients ≥60 years)												
1	randomised trials	not serious	not serious	serious [c]	serious [d]	none	10/125 (8.0%)	7/135 (5.2%)	**RR 1.54** (0.61 to 3.93)	**28 more per 1.000** (from 20 fewer to 152 more)	⨁⨁◯◯ LOW	CRITICAL
Hospital mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
3	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	81/2667 (3.0%)	94/2676 (3.5%)	**RR 0.88** (0.48 to 1.62)	**4 fewer per 1.000** (from 18 fewer to 22 more)	⊕⊕⊕◯ MODERATE	CRITICAL
90-day mortality												
1	randomised trials	not serious	not serious	serious [e]	serious [b]	none	42/1000 (4.2%)	26/1003 (2.6%)	**RR 1.62** (1.00 to 2.62)	**16 more per 1.000** (from 0 fewer to 42 more)	⊕⊕◯◯ LOW	CRITICAL
Patients exposed to RBC transfusion												
7	randomised trials	not serious	not serious	not serious	not serious	none	2323/4299 (54.0%)	3324/4299 (77.3%)	**RR 0.69** (0.66 to 0.73)	**240 fewer per 1.000** (from 209 fewer to 263 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
RBC units transfused (mean)												
3	randomised trials	serious [f]	not serious [g]	not serious	not serious	none	272	274	-	MD **0.87 units lower** (1.29 lower to 0.45 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
RBC units transfused (median)												
1	randomised trials	not serious	not serious	serious [h]	not serious	none	2430	2430	-	median **1 unit lower** (0 to 0)	⊕⊕⊕◯ MODERATE	IMPORTANT
Haemoglobin concentration												
1	randomised trials	not serious	not serious	serious [c]	serious [b]	none	249	253	-	MD **1.4 lower** (3.1 lower to 0.3 higher)	⊕⊕◯◯ LOW	IMPORTANT
Cardiac events												
3	randomised trials	serious [f]	not serious	serious [i]	not serious	none	108/481 (22.5%)	109/487 (22.4%)	**RR 0.99** (0.75 to 1.30)	**2 fewer per 1.000** (from 56 fewer to 67 more)	⊕⊕◯◯ LOW	CRITICAL
Myocardial infarction												
6	randomised trials	not serious	not serious	serious [i]	not serious	none	150/3712 (4.0%)	149/3709 (4.0%)	**RR 1.00** (0.81 to 1.25)	**0 fewer per 1.000** (from 8 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Congestive heart failure												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [f]	not serious	serious [j]	serious [d]	none	0/20 (0.0%)	1/18 (5.6%)	**RR 0.30** (0.01 to 6.97)	**39 fewer per 1.000** (from 55 fewer to 332 more)	⨁◯◯◯ VERY LOW	IMPORTANT
CVA-stroke												
6	randomised trials	not serious	not serious	serious [i]	serious [b]	none	80/4074 (2.0%)	84/4064 (2.1%)	**RR 0.94** (0.69 to 1.28)	**1 fewer per 1.000** (from 6 fewer to 6 more)	⨁⨁◯◯ LOW	CRITICAL
Rebleeding												
3	randomised trials	not serious	not serious	serious [i]	serious [b]	none	25/1261 (2.0%)	29/1260 (2.3%)	**RR 0.87** (0.51 to 1.48)	**3 fewer per 1.000** (from 11 fewer to 11 more)	⨁⨁◯◯ LOW	IMPORTANT
Sepsis-bacteraemia												
3	randomised trials	not serious	not serious	very serious [k]	not serious	none	217/1008 (21.5%)	210/1007 (20.9%)	**RR 1.02** (0.87 to 1.21)	**4 more per 1.000** (from 27 fewer to 44 more)	⨁⨁◯◯ LOW	IMPORTANT
Pneumonia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [h]	serious [d]	none	4/25 (16.0%)	0/25 (0.0%)	**RR 9.00** (0.51 to 158.85)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Pneumonia or wound infection												
4	randomised trials	not serious	not serious	serious [i]	not serious	none	394/3825 (10.3%)	369/3852 (9.6%)	**RR 1.07** (0.94 to 1.22)	**7 more per 1.000** (from 6 fewer to 21 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Thromboembolism												
2	randomised trials	not serious	not serious	serious [k]	serious [b]	none	10/1010 (1.0%)	12/1006 (1.2%)	**RR 0.82** (0.36 to 1.88)	**2 fewer per 1.000** (from 8 fewer to 10 more)	⊕⊕◯◯ LOW	IMPORTANT
Renal failure												
6	randomised trials	not serious	not serious	serious [i]	not serious	none	231/4266 (5.4%)	224/4266 (5.3%)	**RR 1.04** (0.87 to 1.24)	**2 more per 1.000** (from 7 fewer to 13 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Renal failure (subgroup: patients <60 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [i]	serious [d]	none	4/124 (3.2%)	3/118 (2.5%)	**RR 1.27** (0.29 to 5.55)	**7 more per 1.000** (from 18 fewer to 116 more)	⊕⊕◯◯ LOW	CRITICAL
Renal failure (subgroup: patients ≥60 years)												
1	randomised trials	not serious	not serious	serious [i]	serious [d]	none	6/125 (4.8%)	10/135 (7.4%)	**RR 0.65** (0.24 to 1.73)	**26 fewer per 1.000** (from 54 more to 56 fewer)	⊕⊕◯◯ LOW	CRITICAL
Health-related quality of life EQ-5D at 6 weeks												
1	randomised trials	not serious	not serious	very serious [e]	not serious	none	1000	1003	-	MD **0.01 points higher** (0.02 lower to 0.03 higher)	⊕⊕◯◯ LOW	IMPORTANT
Health-related quality of life EQ-5D at 3 months												
1	randomised trials	not serious	not serious	very serious [e]	not serious	none	1000	1003	-	MD **0 points** (0.03 lower to 0.02 higher)	⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospital mortality or multisystem organ failure												
1	randomised trials	not serious	not serious	serious [l]	serious [d]	none	3/363 (0.8%)	6/354 (1.7%)	**RR 0.49** (0.12 to 1.93)	**9 fewer per 1.000** (from 15 fewer to 16 more)	⊕⊕◯◯ LOW	CRITICAL
Vascular morbidity (aortic or femoral artery dissection or acute limb ischaemia)												
1	randomised trials	not serious	not serious	serious [l]	serious [d]	none	0/363 (0.0%)	3/354 (0.8%)	**RR 0.14** (0.01 to 2.69)	**7 fewer per 1.000** (from 8 fewer to 14 more)	⊕⊕◯◯ LOW	IMPORTANT
Pulmonary morbidity (pneumonia, pulmonary embolus or prolonged postoperative ventilation >24 hours)												
1	randomised trials	not serious	not serious	serious [l]	serious [d]	none	23/363 (6.3%)	19/354 (5.4%)	**RR 1.18** (0.65 to 2.13)	**10 more per 1.000** (from 19 fewer to 61 more)	⊕⊕◯◯ LOW	IMPORTANT
Gastrointestinal morbidity												
1	randomised trials	not serious	not serious	serious [l]	serious [d]	none	5/363 (1.4%)	2/354 (0.6%)	**RR 2.44** (0.48 to 12.48)	**8 more per 1.000** (from 3 fewer to 65 more)	⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7.5/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <9-10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reoperative morbidity (for bleeding/tamponade, graft occlusion, valve dysfunction)												
1	randomised trials	not serious	not serious	serious [l]	serious [d]	none	9/363 (2.5%)	10/354 (2.8%)	**RR 0.88** (0.36 to 2.13)	**3 fewer per 1.000** (from 18 fewer to 32 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Decision not to downgrade by reviewer(s) although Bracey, 1999 has serious limitations. However, for these outcomes the results from Bracey do not have much influence on the point estimate and 95% CI as the study is assigned little weight; b. Large variability in results; c. Lack of generalizibility: evidence from 1 Brazilian study; d. Low number of events, limited sample size and large variability in results; e. Lack of generalizibility: evidence from 1 UK study; f. Selection bias and detection bias; g. Decision not to downgrade by reviewer(s) although point estimates vary, CIs show minimal or no overlap, tests for heterogeneity show a low p-value and I2>75%. This large inconsistency or variability is, however, not considered important as the direction of effect is the same for all studies which is most relevant for this outcome; h. Lack of generalizibility: evidence from 1 Canadian study; i. Lack of generalizibility: variation in outcome definitions; j. Lack of generalizibility: evidence from 1 (old) USA study; k. Lack of generazibility: variation in outcome definitions and evidence from only 2 studies; l. Lack of generalizibility: evidence from 1 USA study.

Detailed evidence summary (PICO 9)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients undergoing cardiac surgery (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. <u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017): #1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD] #2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST] #3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)) #4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)) #5 (blood near/3 (management or program*)) #6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti #7 #1 or #2 or #3 or #4 or #5 or #6 **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4

	Embase (via Embase.com interface) using the following search strategy (from 27th May 2016 until 30th June 2017): #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 **Transfusion evidence library** (from 2016 until 2017) Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: adult patients undergoing cardiac surgery. **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** Systematic reviews (+ meta-analyses) of experimental studies (RCT's). If systematic reviews (published within 5 years of the search date) are not available, we will search for individual experimental studies (RCT's). To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also

	known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes**.**

Characteristics of included studies

Author, year, country	Study design	Population	Comparison	Study funding, financial COI and remarks
Bracey, 1999, USA	Experimental: Randomised controlled trial	428 consecutive participants undergoing elective primary coronary artery bypass graft surgery (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=216, 179 males and 37 females (M/F ratio = 83/17), age=62±11 years Liberal group: n=212, 174 males and 38 females (M/F ratio = 82/18), age=61±11 years	Restrictive group: transfusion in the postoperative period at a Hb level <8.0 g/dL Liberal group: on the instructions of the individual physician who considered clinical assessment of the patient and the institutional guidelines, which proposed a Hb level <9.0 g/dL as the postoperative threshold for RBC transfusion Transfusion: RBC units	No information provided on study funding or conflicts of interest. Identified from the systematic review of Carson et al., 2016.
Hajjar, 2010, Brazil	Experimental: Randomised controlled trial	502 adult participants who underwent cardiac surgery with cardiopulmonary bypass (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=249, 149 males and 100 females, age=58.6±12.5 years Liberal group:	Restrictive group: transfusion if haematocrit <24% (~Hb level <8 g/dL) Liberal group: transfusion if haematocrit <30% (~Hb level <10 g/dL) at any time from start of the surgery until discharge from ICU Transfusion:	Financial disclosures: none reported. Identified from the systematic review of Carson et al., 2016. The substudy Nakamura et al., 2015 (with subpopulations ≥60 years and >60 years) was

		n=253, 161 males and 92 females, age=60.7±12.5 years	allogeneic RBC transfusions	identified from the systematic review Lelubre in the search update.
Johnson, 1992, USA	Experimental: Randomised controlled trial	39 autologous blood donors undergoing elective myocardial revascularisation (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=20, 20 males, age=58.2±7.5 years Liberal group: n=18, 16 males and 2 females, age=60.5±6.9 years	Restrictive group: transfusion if post-operative haematocrit <25% (~Hb level <8.33 g/dL) Liberal group: transfusion to achieve post-operative haematocrit of 32% (~Hb level <10.67 g/dL) as long as autologous blood was available Transfusion: Autologous blood; sequestration of one or more units autologous blood in patients with haematocrit >35% after anaesthetic induction	One of the authors is supported in part by an NIH award. Identified from the systematic review of Carson et al., 2016.
Koch, 2017, USA	Experimental: Randomised controlled trial	717 adults undergoing CABG surgery or valve procedures (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=363, 63% males, age=59±15 years Liberal group: n=354, 66% males, age=60±13 years	Restrictive group: transfusion if haematocrit <24% (= +/- 8 g/dL) Liberal group: transfusion if haematocrit <28% (= +/- 9.3 g/dL) Transfusion: One unit of red blood cells was transfused if the hematocrit fell below the designated threshold.	This study was supported in part by the Gus P. Karos Registry Fund, the Kenneth Gee and Paula Shaw, PhD, Chair in Heart Research (EHB), and the Sheikh Hamdan bin Rashid Al Maktoum Distinguished Chair in Thoracic and Cardiovascular Surgery (JFS).
Laine, 2017, Finland	Experimental: Randomised controlled trial	80 patients scheduled for non-emergency coronary artery bypass grafting simple one valve (aortic or	Restrictive group: transfusion if Hb <8.0 g/dL until above this threshold	Trial was supported by a government and by the Finnish

		mitral) replacement or both, requiring cardiopulmonary bypass Restrictive group: n=40, 29 males and 11 females, age (95% confidence interval)=70.5 (67.8-73.2) years Liberal group: n= 40, 28 males and 12 females, age (95% confidence interval)=64.5 (60.6-68.3) years	Liberal group: transfusion if Hb <10.0 g/dL until above this threshold Transfusion: Packed RBC	Angiological Society. Two authors received travel reimbursements from companies, one of which is the supplier of tests used in the experiment. Identified through search update.
Mazer, 2017, Canada	Experimental: Randomised controlled trial	Participants (from 19 countries across the world) older than 18 years of age scheduled to undergo cardiac surgery with cardiopulmonary bypass and who had a preoperative additive EuroSCORE I of 6 or higher (predictive of in-hospital mortality >4%) Restrictive group: n=2430, 1553 males and 877 females, age=72±10 years Liberal group: n=2430, 1586 males and 844 females, age=72±10 years	Restrictive group: transfusion if Hb <7.5 g/dL intraoperatively or postoperatively Liberal group: transfusion if Hb <9.5 g/dL intraoperatively or postoperatively in ICU or if Hb <8.5 g/dL in non-ICU ward Transfusion: allogeneic red cells	Trial was supported by the Canadian Institutes of Health Research, the Canadian Blood Services–Health Canada, the National Health and Medical Research Council of Australia, and the Health Research Council of New Zealand TRICS II and TRIC III trial Identified through search update.
Murphy, 2015, UK	Experimental: Randomised controlled trial	Participants older than 16 years of age who were undergoing nonemergency cardiac surgery with haemoglobin level below 9 g/dL (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=1000, 693 males and 307 females, median age (interquartile range)=69.9 (63.1-76.0) years	Restrictive group: transfusion if post-surgery Hb level <7.5 g/dL Liberal group: transfusion if post-surgery Hb level <9.0 g/dL Transfusion: Red cells units	Research supported by government program (National Institute for Health Research NIHR)). One author and one research nurse team were supported in part by NIHR research unit. Three authors were supported by the

		Liberal group: n=1003, 680 males and 323 females, median age (interquartile range)=70.8 (64.1-76.7) years		British Heart Foundation (a charitable organisation). No conflicts of interest reported. Identified from the systematic review of Carson et al., 2016. Two additional reports (Reeves, 2016 (full report) and Stokes, 2016 (CBA)) identified from search update.
Shehata, 2012, Canada	Experimental: Randomised controlled trial	Adult participants undergoing cardiac surgery with a CARE score (a score for cardiac surgery participants used to predict morbidity and mortality) of 3 or 4, or participants of advanced age defined as greater than or equal to 80 years (clinical specialty subgroup (Carson, 2016): cardiac surgery) Restrictive group: n=25, 17 males and 8females, age=67.2±11.2 years Liberal group: n=25, 20 males and 5 females, age=68.8±9.2 years	Restrictive group: RBC transfusions if Hb ≤7.0 g/dL during cardiopulmonary bypass and ≤7.5 g/dL postoperatively Liberal group: RBC transfusions if Hb ≤ 9.5 g/dL during cardiopulmonary bypass and ≤10 g/dL postoperatively Transfusion: RBC units	Study supported by Canadian Blood Service (charitable organization). Authors declared that they have no conflicts of interest. Identified from the systematic review of Carson et al., 2016.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Primary outcomes				
30-day mortality	Restrictive vs liberal transfusion threshold	Not statistically significant: 44/1464 vs 38/1478 RR: 1.18, 95%CI [0.77;1.81]¥ (p=0.46) (Figure 78)	3, 1464 vs 1478	Bracey 1999, Hajjar 2010, Murphy 2015

		Subgroup analysis Hajjar 2010: Participants <60 years: Not statistically significant: 5/124 vs 5/118 § RR: 0.95, 95%CI [0.28;3.20]¥ (p=0.94)**	1, 124 vs 118	Hajjar 2010 (data from Nakamura 2016 identified in search update)
		Subgroup analysis Hajjar 2010: Participants ≥60 years: Not statistically significant: 10/125 vs 7/135 § RR: 1.54, 95%CI [0.61;3.93]¥ (p=0.36)**	1, 125 vs 135	Hajjar 2010 (data from Nakamura 2016 identified in search update)
Hospital mortality		Not statistically significant: 81/2667 vs 94/2676 RR: 0.88, 95%CI [0.48;1.62]¥ (p=0.69)** (Figure 79)	3, 2667 vs 2676	Bracey 1999, Mazer 2017, Shehata 2012
Hospital mortality or multisystem organ failure		Not statistically significant: 3/363 vs 6/354 § RR: 0.49, 95%CI [0.12;1.93]¥ (p=0.31)** (Figure 3)	1, 363 vs 354	Koch, 2017
90-day mortality		Not statistically significant: 42/1000 vs 26/1003 RR: 1.62, 95%CI [1.00;2.62]¥ (p=0.05)* (Figure 4)	1, 1000 vs 1003	Murphy 2015
Participants exposed to blood transfusion		Statistically significant: 2323/4299 vs 3324/4299 RR: 0.69, 95%CI [0.66;0.73] (p<0.00001)** (Figure 5) *In favour of restrictive transfusion threshold*	7, 4299 vs 4299	Bracey 1999, Hajjar 2010, Johnson 1992, Koch 2017, Mazer 2017, Murphy 2015, Shehata 2012
Units of blood transfused		Statistically significant: MD: -0.87, 95%CI [-1.29;-0.45] (p<0.0001)** (Figure 6) *In favour of restrictive transfusion threshold*	3, 272 vs 274	Bracey 1999, Johnson 1992, Laine 2017
		Statistically significant: Median (IQR): 2 (1-4) vs 3 (2-5) Rate Ratio: 0.85, 95%CI [0.82;0.88] (p<0.05)	1, 2430 vs 2430	Mazer 2017
Secondary outcomes				
Haemoglobin concentration	Restrictive vs liberal transfusion threshold	Not statistically significant: 9.4±10.5 vs 10.8±8.9 MD: -1.40, 95%CI [-3.10;0.30] (p=0.11)* (Figure 7)	1, 249 vs 253	Hajjar 2010
Cardiac events		Not statistically significant: 108/481 vs 109/487 RR: 0.99, 95%CI [0.75;1.30]¥ (p=0.93)* (Figure 8)	3, 481 vs 487	Bracey 1999, Hajjar 2010, Johnson 1992
Myocardial infarction		Not statistically significant: 150/3712 vs 149/3709 RR: 1.00, 95%CI [0.81;1.25]	6, 3712 vs 3709	Bracey 1999, Johnson 1992,

		(p=0.97)** (Figure 9)		Laine 2017, Mazer 2017, Murphy 2015, Shehata 2012
Congestive heart failure		Not statistically significant: 0/20 vs 1/18 § RR: 0.30, 95%CI [0.01;6.97] ¥ (p=0.45)* (Figure 10)	1, 20 vs 18	Johnson 1992
Cerebrovascular accident (CVA) - stroke		Not statistically significant: 80/4074 vs 84/4064 RR: 0.94, 95%CI [0.69;1.28] ¥ (p=0.70)** (Figure 8011)	6, 4074 vs 4064	Hajjar 2010, Johnson 1992, Koch 2017 Mazer 2017, Murphy 2015, Shehata 2012
Rebleeding		Not statistically significant: 25/1261 vs 29/1260 RR: 0.87, 95%CI [0.51;1.48] ¥ (p=0.61)** (Figure 2)	3, 1261 vs 1260	Hajjar 2010, Murphy 2015 (data from Reeves 2016 identified in search update), Shehata 2012
Vascular morbidity (aortic or femoral artery dissection or acute limb ischaemia)		Not statistically significant: 0/363 vs 3/354 RR: 0.14, 95%CI [0.01;2.69] ¥ (p=0.19)* (Figure 3)	1, 363 vs 354	Koch 2017
Sepsis-bacteraemia		Not statistically significant: 218/1371 vs 211/1361 RR: 1.02, 95%CI [0.87;1.21] ¥ (p=0.78)* (Figure 4)	3, 1371 vs 1361	Koch 2017, Murphy 2015, Shehata 2012
Pneumonia		Not statistically significant: 4/25 vs 0/25 § RR: 9.00, 95%CI [0.51;158.85] ¥ (p=0.13)* (Figure 5)	1, 25 vs 25	Shehata 2012
Pneumonia or wound infection		Not statistically significant: 394/3825 vs 369/3852 RR: 1.07, 95%CI [0.94;1.22] (p=0.29)** (Figure 6)	4, 3825 vs 3852	Bracey 1999, Hajjar 2010, Mazer 2017, Murphy 2015
Pulmonary morbidity (pneumonia, pulmonary embolus or prolonged postoperative ventilation >24 hours)		Not statistically significant: 23/363 vs 19/354 § RR: 1.18, 95%CI [0.65;2.13] ¥ (p=0.58)** (Figure 17)	1, 363 vs 354	Koch, 2017
Thromboembolism		Not statistically significant: 10/1010 vs 12/1006 RR: 0.82, 95%CI [0.36;1.88] ¥ (p=0.64)** (Figure 8118)	2, 1010 vs 1006	Murphy 2015 (data from Reeves 2016 identified in search update), Shehata 2012
Renal failure		Not statistically significant: 231/4266 vs 224/4266 RR: 1.04, 95%CI [0.87;1.24] (p=0.66)** (Figure 8219)	6, 4266 vs 4266	Bracey 1999, Hajjar 2010, Koch 2017, Mazer 2017,

				Murphy 2015, Shehata 2012
		Subgroup analysis Hajjar 2010: Participants <60 years: Not statistically significant: 4/124 vs 3/118 § RR: 1.27, 95%CI [0.29;5.55]¥ (p=0.75)**	1, 124 vs 118	Hajjar 2010 (data from Nakamura 2016 identified in search update)
		Subgroup analysis Hajjar 2010: Participants ≥60 years: Not statistically significant: 6/125 vs 10/135 § RR: 0.65, 95%CI [0.24;1.73]¥ (p=0.39)**	1, 125 vs 135	Hajjar 2010 (data from Nakamura 2016 identified in search update)
Gastrointestinal morbidity		Not statistically significant: 5/363 vs 2/354 § RR: 2.44, 95%CI [0.48;12.48] ¥ (p=0.28)* (Figure 20)	1, 363 vs 354	Koch, 2017
Reoperative morbidity (for bleeding/tamponade, graft occlusion, valve dysfunction)		Not statistically significant: 9/363 vs 10/354 § RR: 0.88, 95%CI [0.36;2.13] ¥ (p=0.77)* (Figure 21)	1, 363 vs 354	Koch, 2017
Health-related quality of life EQ-5D at 6 weeks		Not statistically significant: 0.692±0.253 vs 0.686±0.253 MD: 0.01, 95%CI [-0.02;0.03] (p=0.60)** (Figure 22)	1, 1000 vs 1003	Murphy 2015 (data from Stokes 2016 identified in search update)
Health-related quality of life EQ-5D at 3 months		Not statistically significant: 0.748±0.285 vs 0.750±0.253 MD: 0.00, 95%CI [-0.03;0.02] (p=0.87)** (Figure 23)		

Mean ± SD (unless otherwise indicated)
CI: confidence interval, RR: relative risk, MD: mean difference, IQR: interquartile range
* Calculations (p-value) done by the reviewer(s) using Review Manager software
** Calculations (RR or MD, 95% CI and p-value) done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Forest Plots

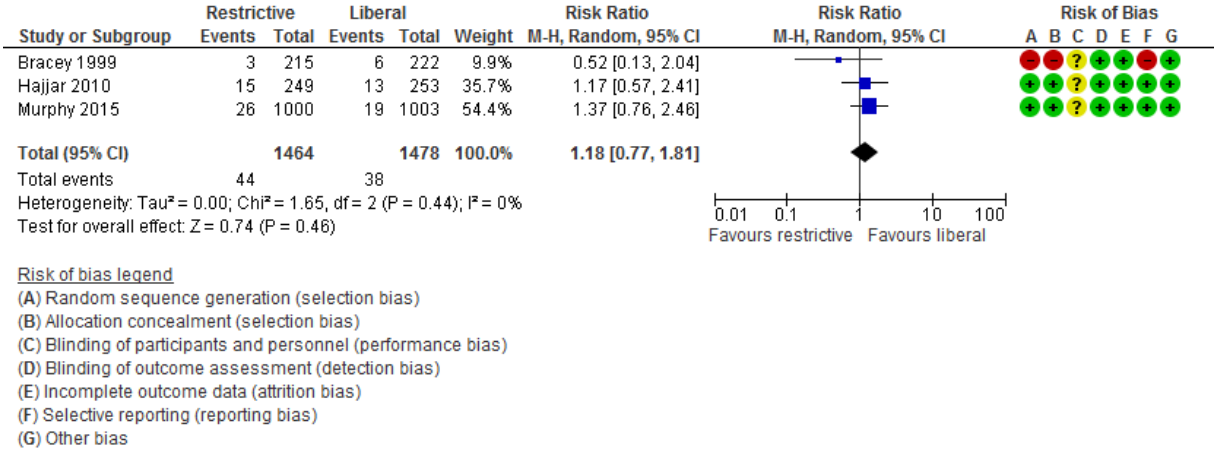


Figure 78: Forest plot of outcome: 30-day mortality. Two subgroup analysis for Hajjar 2010 (participants <60 years and participants ≥60 years respectively can be found in the synthesis of findings table).

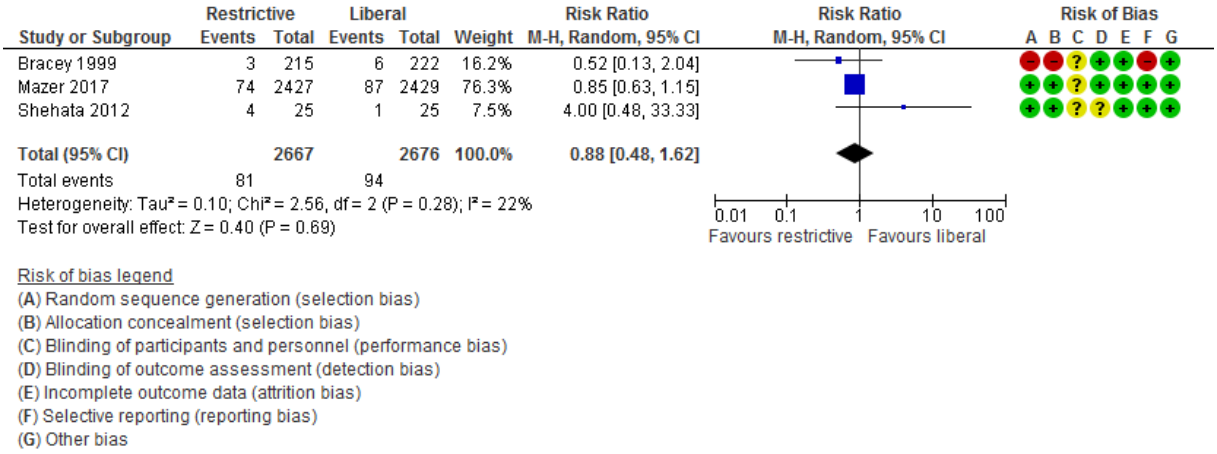


Figure 79: Forest plot of outcome: Hospital mortality.

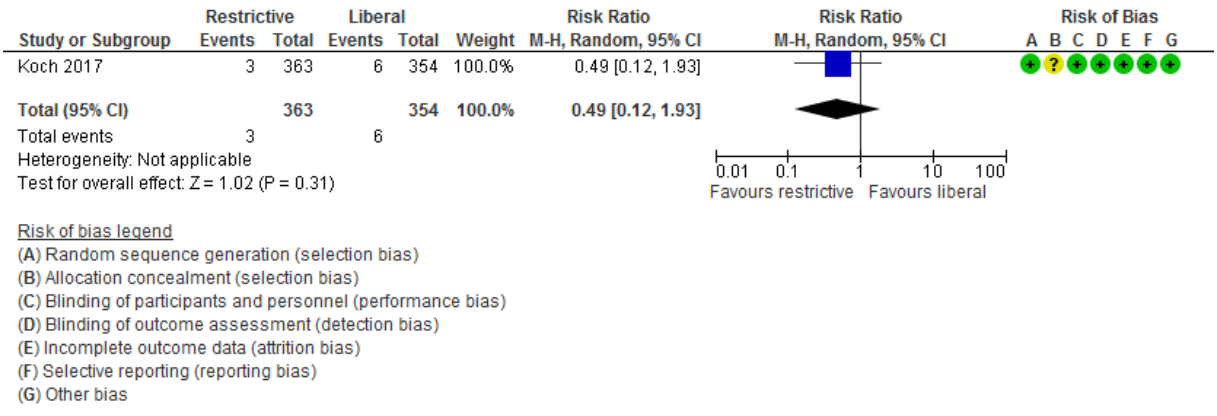


Figure 3: Forest plot of outcome: Hospital mortality or multisystem organ failure.

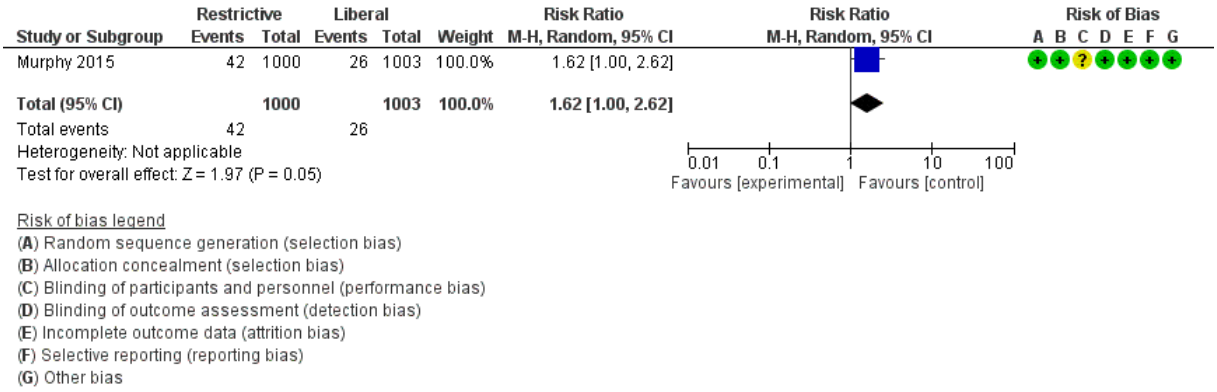


Figure 4: Forest plot of outcome: 90-day mortality.

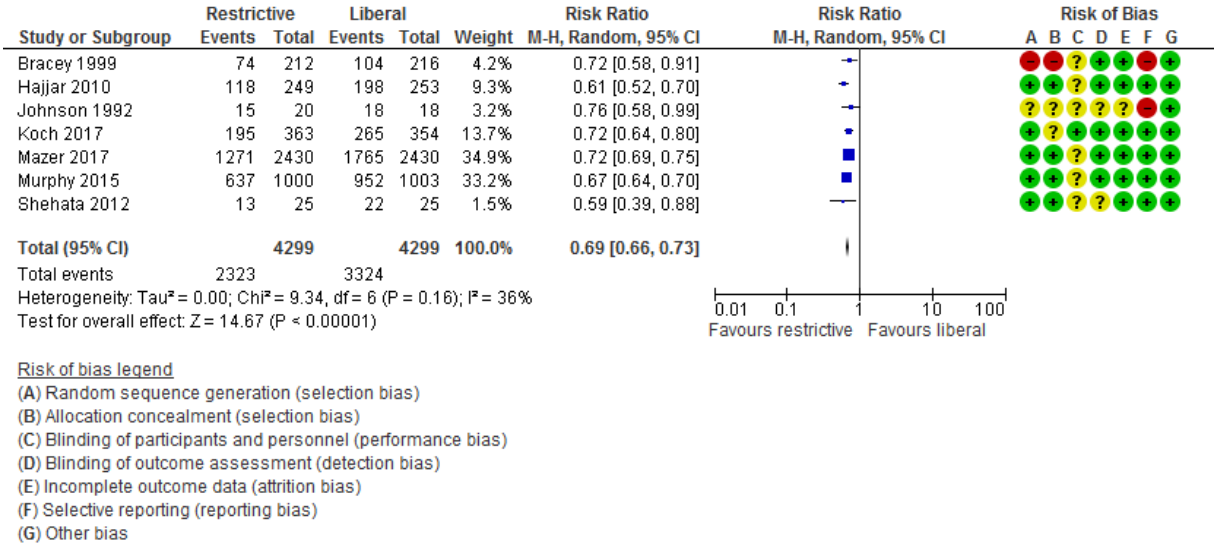


Figure 5: Forest plot of outcome: Participants exposed to blood transfusion.

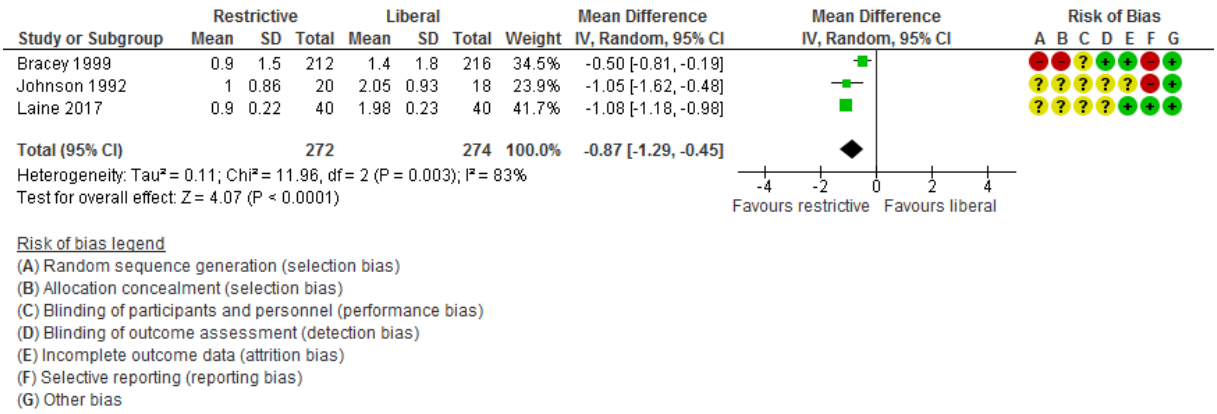


Figure 6: Forest plot of outcome: Units of blood transfused.

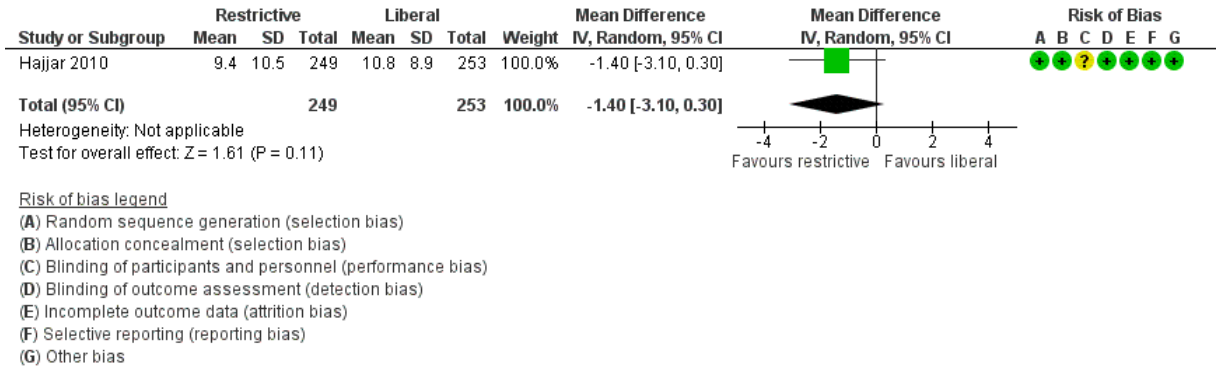


Figure 7: Forest plot of outcome: Haemoglobin concentration.

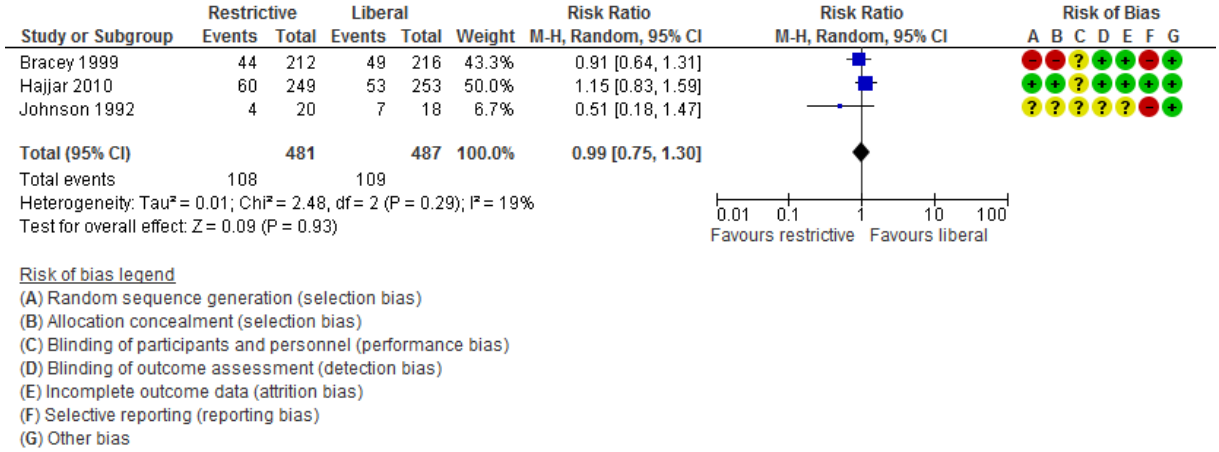


Figure 8: Forest plot of outcome: Cardiac events.

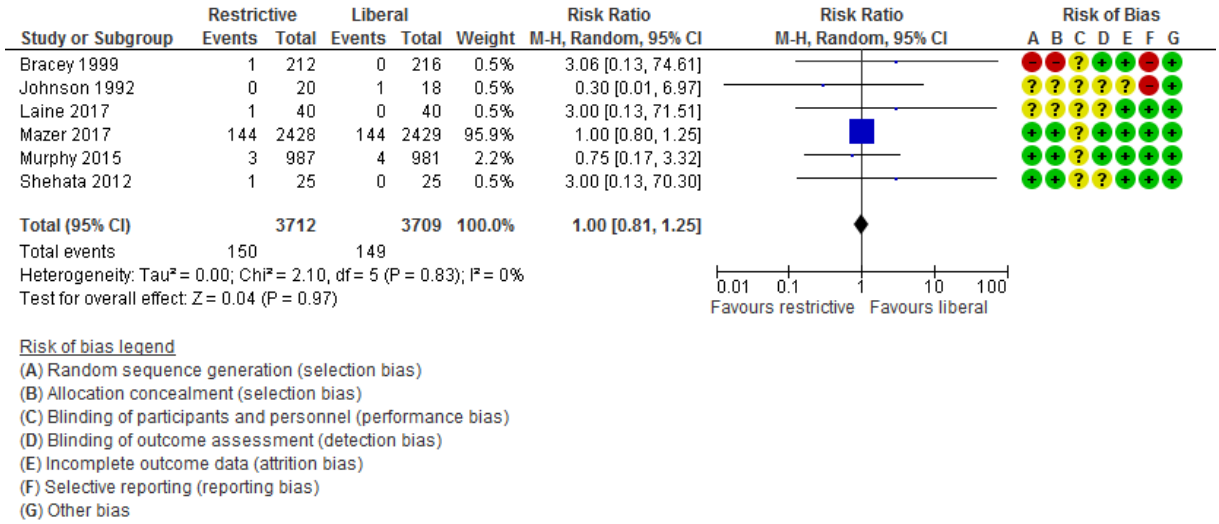


Figure 9: Forest plot of outcome: Myocardial infarction.

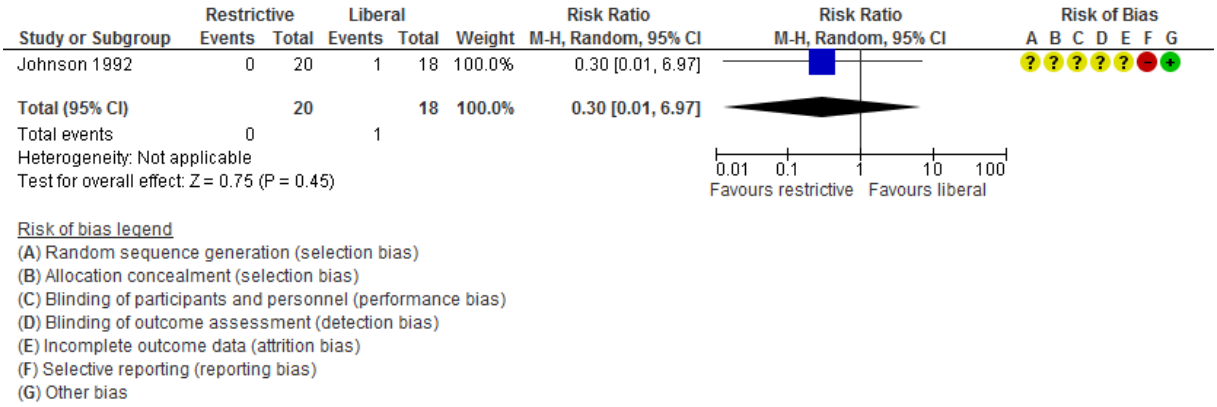


Figure 10: Forest plot of outcome: Congestive heart failure.

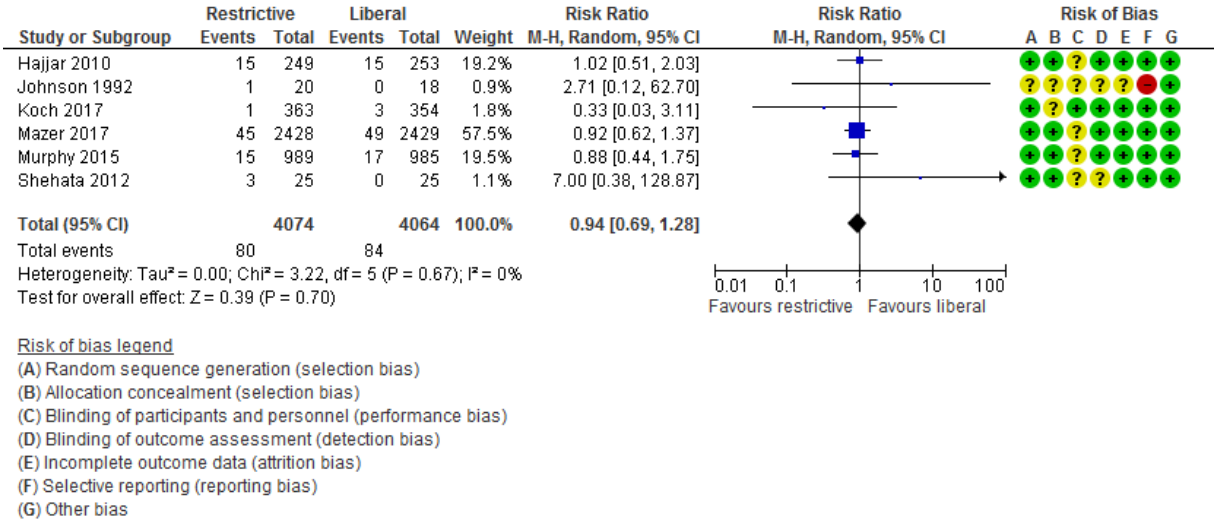


Figure 801: Forest plot of outcome: Cerebrovascular accident (CVA) - stroke.

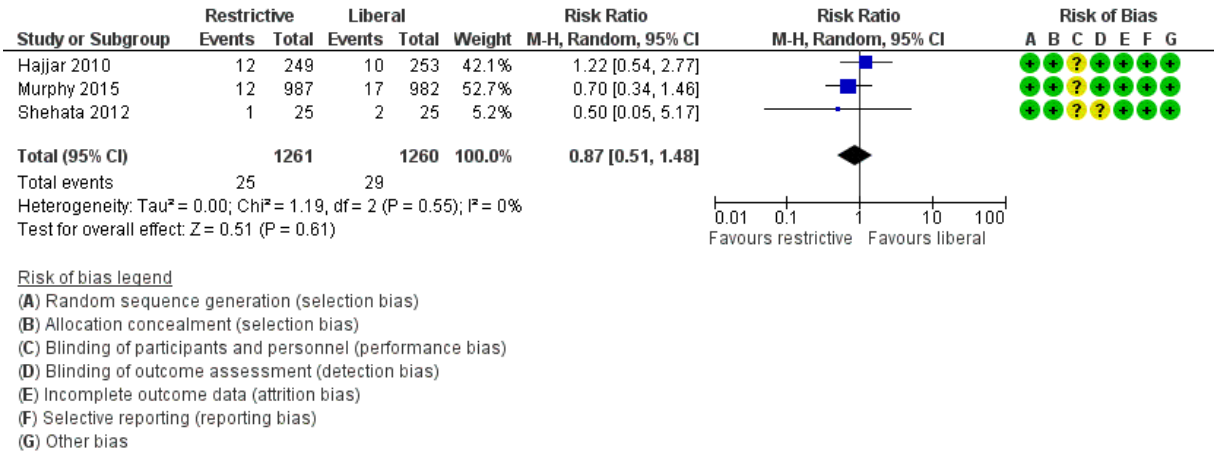


Figure 12: Forest plot of outcome: Rebleeding.

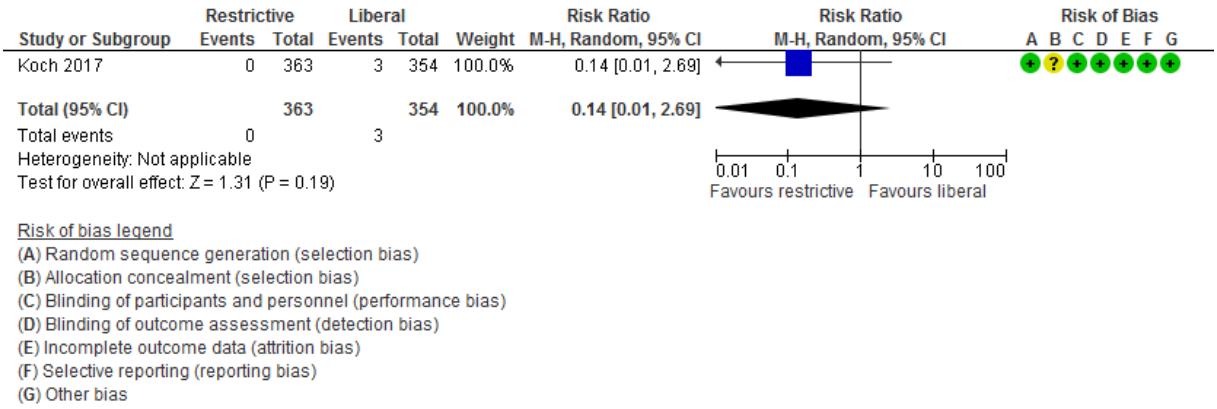


Figure 13: Forest plot of outcome: Vascular morbidity (aortic or femoral artery dissection or acute limb ischaemia).

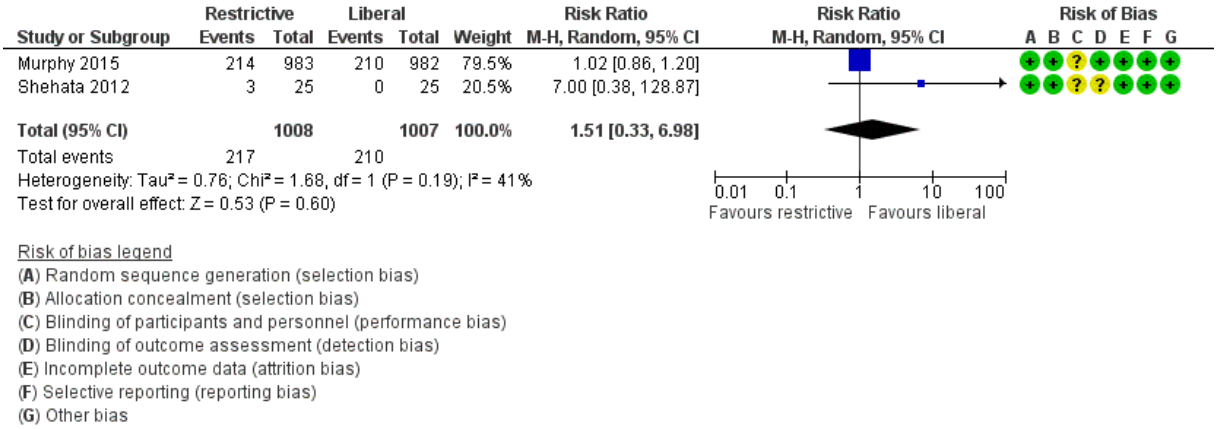


Figure 14: Forest plot of outcome: Sepsis-bacteraemia.

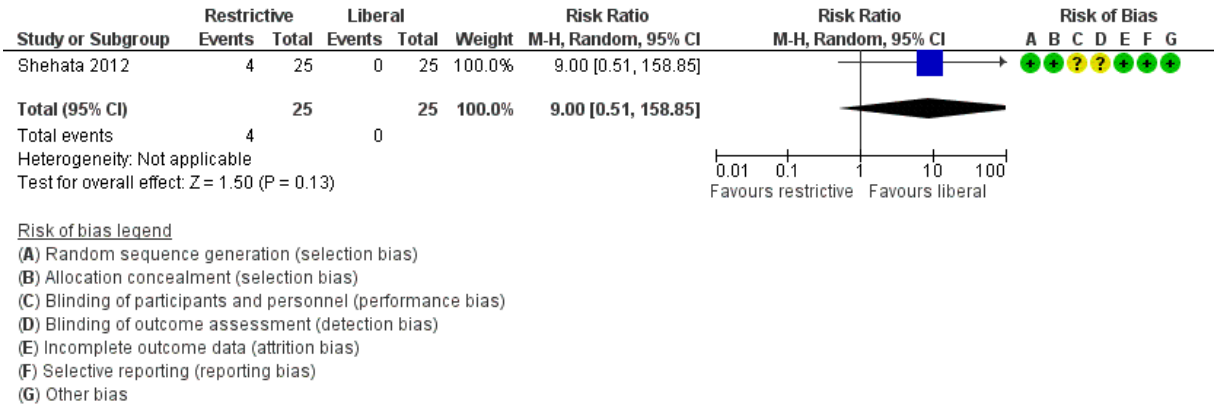


Figure 15: Forest plot of outcome: Pneumonia.

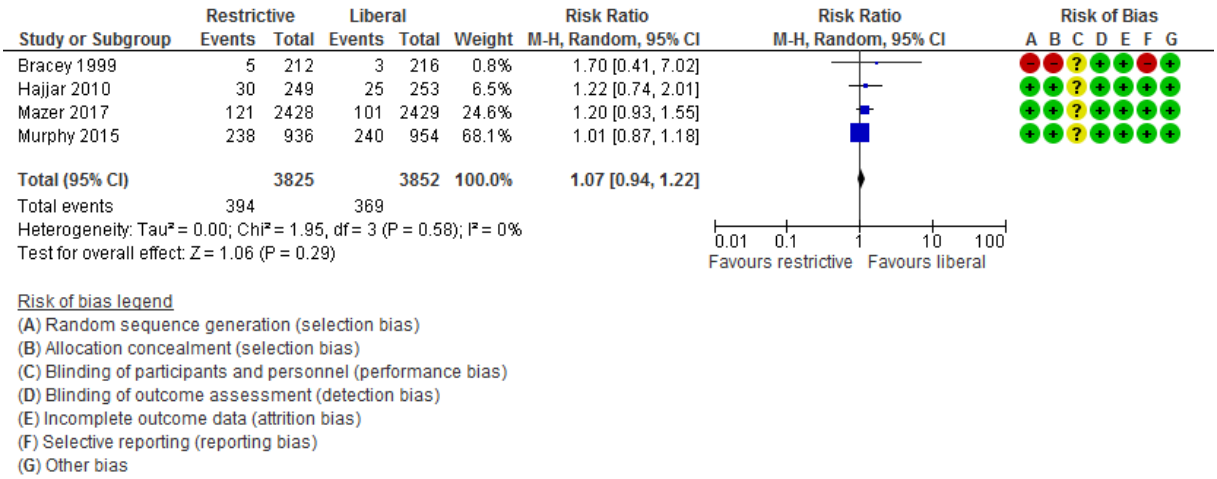


Figure 16: Forest plot of outcome: Pneumonia or wound infection.

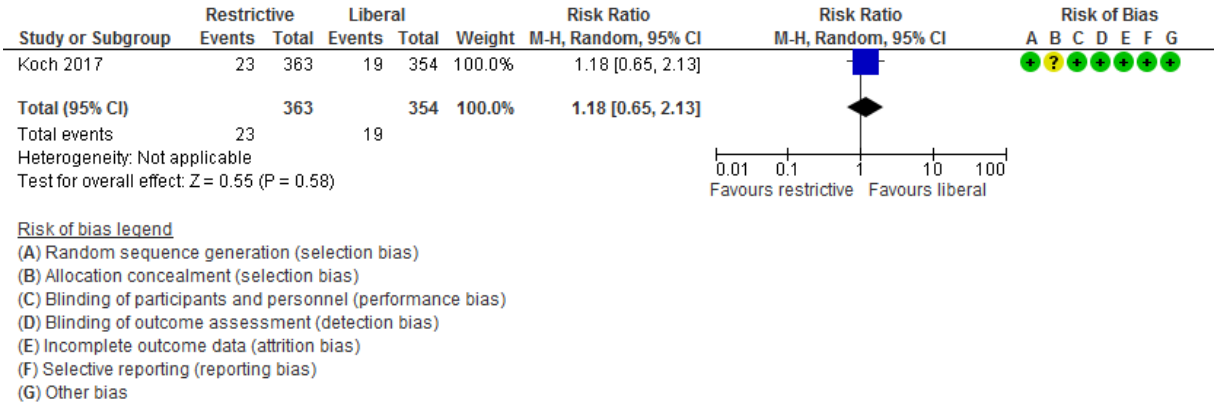


Figure 17: Forest plot of outcome: Pulmonary morbidity (pneumonia, pulmonary embolus, or prolonged postoperative ventilation >24 hours).

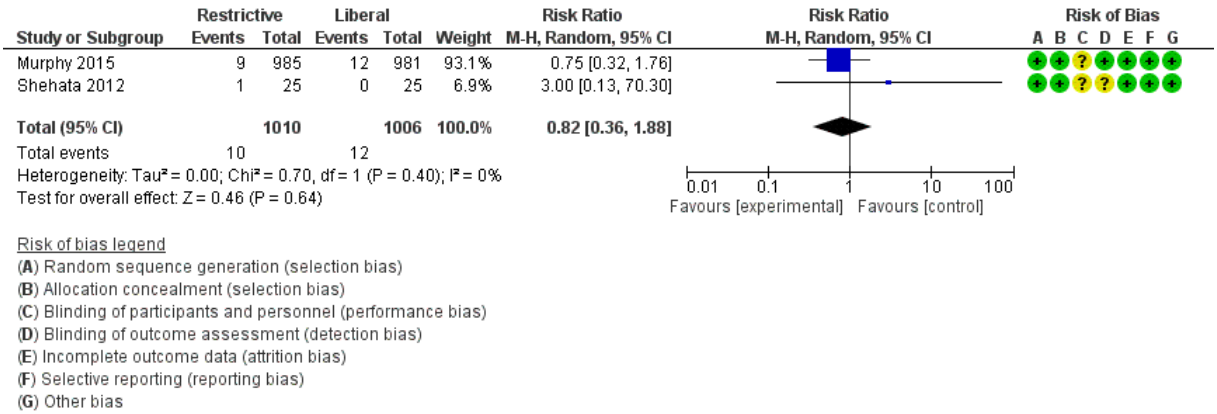


Figure 818: Forest plot of outcome: Thromboembolism

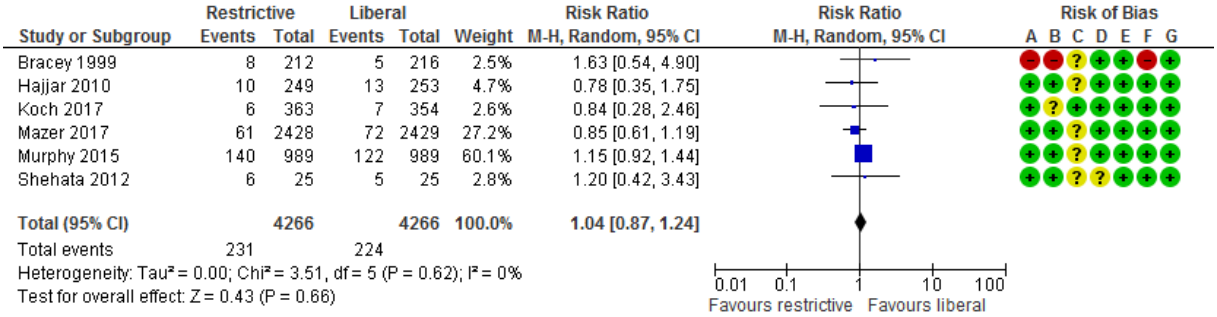


Figure 829: Forest plot of outcome: Renal failure. Two subgroup analysis for Hajjar 2010 (participants <60 years and participants ≥60 years respectively) can be found in the synthesis of findings table.

Figure 20: Forest plot of outcome: Gastrointestinal morbidity.

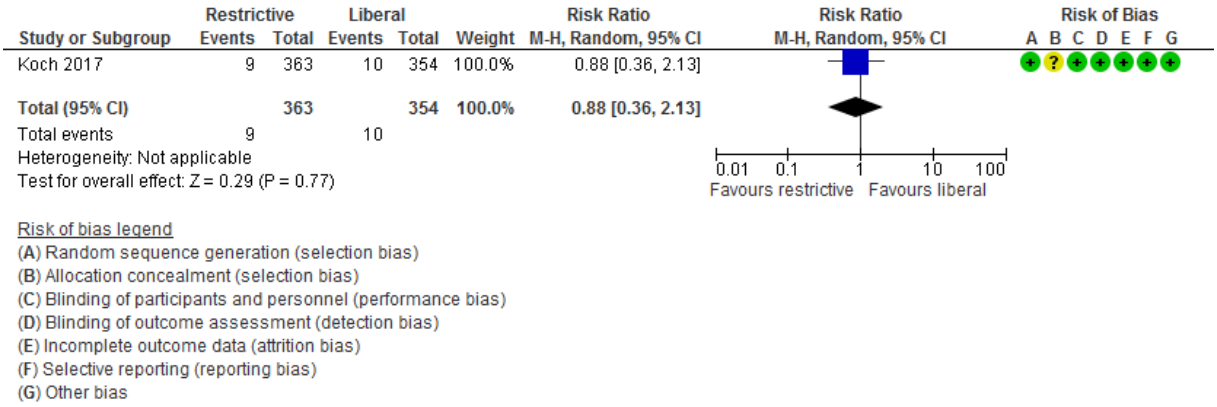


Figure 21: Forest plot of outcome: Reoperative morbidity.

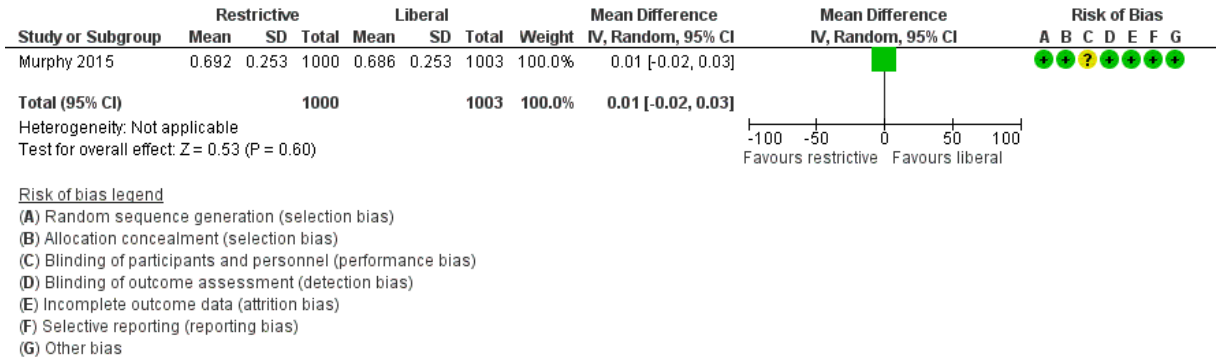


Figure 22: : Forest plot of outcome: Health-related quality of life EQ-5D at 6 weeks.

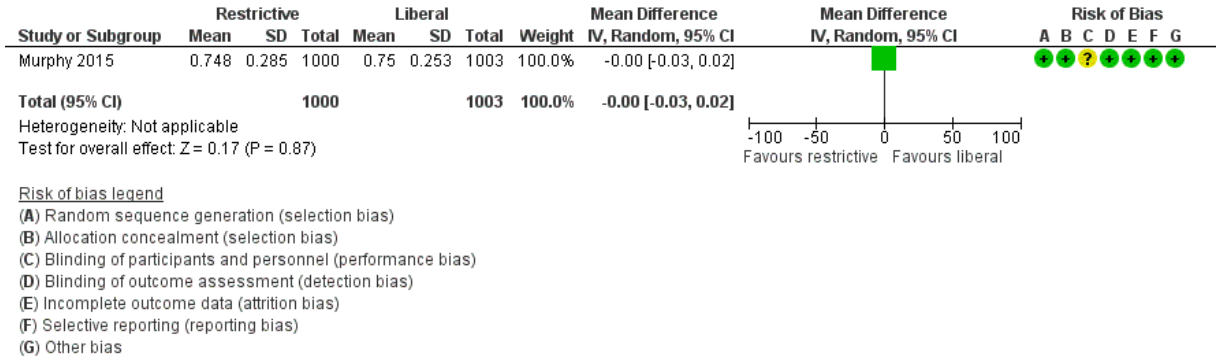


Figure 23: : Forest plot of outcome: Health-related quality of life EQ-5D at 3 months.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Bracey, 1999	Randomization: Yes, participants were randomly assigned on the basis of the last digit of their medical record number. Allocation concealment: Yes, inadequate concealment (record number).	Participants and personnel: Unclear, no information provided. Outcome assessors: No, outcome of mortality allows a judgement of low risk of bias. Morbidity information was collected from the hospital database. The trial provided no information regarding the survey questionnaire	No, trial used intention-to-treat analysis and reported the exclusion of a small number of participants.	Yes No pre-registration of study protocol	No
Hajjar, 2010	Randomization: No, chief statistician prepared a random number table to use. Allocation concealment: No, opaque envelopes were opened sequentially.	Participants and personnel: Unclear, participants were blinded but clinicians were not. Outcome assessors: No, assessor was blinded.	No, intention-to-treat analysis was undertaken. Follow-up was complete.	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT01021631)	No
Johnson, 1992	Randomization: Unclear, a table of random numbers and an odd-even designation randomized participants. Allocation concealment: Unclear, no information provided.	Participants and personnel: Unclear, surgeons and anaesthesiologists were blinded as to the group of randomisation until the participant reached the intensive care unit (ICU). Outcome assessors: Unclear, no information provided.	Unclear, small number of exclusions were reported.	Yes No pre-registration of study protocol	No
Koch, 2017	Randomization: No, randomization was stratified by	Participants and personnel: No Outcome assessors: No	No, no lost to follow up or discontinued	No Pre-registration	No

	site, using within each site randomly sized blocks of 6, 8, 10, and 12 so that at any given time, approximately equal numbers of patients were randomized into each transfusion trigger group Allocation concealment: unclear, no information provided	Surgeons were blinded to the study arm, as were personnel assessing patient outcomes and the patients themselves.	intervention in both groups.	of study protocol @ ClinicalTrials.Gov (NCT00651573)	
Laine, 2017	Randomization: Unclear, randomization was done in blocks of 20 patients. Allocation concealment: Unclear, closed envelopes were used.	Participants and personnel: Unclear, blinding was not possible. Outcome assessors: Unclear, no information provided.	No, complete follow-up reported.	Unclear Pre-registration of study protocol @ Hospital District of Helsinki and Uusimaa (§94,9.05.2014)	No
Mazer, 2017	Randomization: No, trial used a centralized, Web-based system which stratified according to center, with acomputer-generated random permuted blocks of varying sizes from two to six. Allocation concealment: No, a concealed centralized Web-based system was used.	Participants and personnel: Unclear, it was not possible to use formal blinding of the assigned transfusion strategy with regard to the participants and medical staff. However, participants were not actively informed about the treatment assignment. Outcome assessors: No, outcome adjudicators were unaware of the trial-group assignments.	No, low loss to follow-up.	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT02042898)	No
Murphy, 2015	Randomization: No, internet-based system	Participants and personnel:	No, low loss to follow-up.	No	No

	used with and cohort minimisation to balance assignments according to centre and type of surgery. Allocation concealment: No, trial used an internet-based system that concealed assignments.	Unclear, physicians and nurses were aware of the group assignments. Participants were meant to be unaware of assignment however at discharge 15.1% of patients believed they knew treatment and 75.6% was correct. Outcome assessors: No, outcomes were adjudicated.		Pre-registration of study protocol (Current Controlled Trials number, ISRCTN70923932)	
Shehata, 2012	Randomization: No, randomization sequence was created using permuted blocks of four stratified by age and the Cardiac Anesthesia Risk Score (CARE). Allocation concealment: No, opaque sequential sealed envelopes were opened at the start of surgery.	Participants and personnel: Unclear, clinicians and participants were not blinded. Outcome assessors: Unclear, no information provided.	No, outcome data were complete.	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT00470444)	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **Bracey 1999** Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, et al. *Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome.* Transfusion 1999, 39(10):1070–1077. **Hajjar 2010** *Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, et al. *Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial.* JAMA 2010, 304(14):1559–1567. Nakamura RE, Vincent JL, Fukushima JT, de Almeida JP, Franco RA, Lee Park C, et al. *A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly patients undergoing cardiac surgery.* J Thorac Cardiovasc Surg 2015, 150(5):1314-1320. Identified from systematic review (Lelubre 2016) in search update.

	Johnson 1992 Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, et al. *Comparison of two transfusion strategies after elective operations for myocardial revascularization.* J Thorac Cardiovasc Surg 1992;104(2):307–314. **Koch 2017** Koch CG, Sessler DI, Mascha EJ, Sabik JF, Li L, Duncan AI, Zimmerman NM, Blackstone EH. *A randomized clinical trial of red blood cell transfusion triggers in cardiac surgery*. Ann Thorac Surg 2017;104:1243-1250. **Laine 2017** Laine A, Niemi T, Schramko A. *Transfusion threshold of hemoglobin 80 g/L is comparable to 100 g/L in terms of bleeding in cardiac surgery: a prospective randomized study.* J Cardiothorac Vasc Anesth 2017, pii: S1053-0770(17)30721-8. [Epub ahead of print] **Mazer 2017** Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. *Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery.* N Engl J Med 2017, 377(22):2133-2144. **Murphy 2015** Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. *Liberal or restrictive transfusion after cardiac surgery.* N Engl J Med 2015, 372: 997–1008. *Reeves BC, Pike K, Rogers CA, Brierley RC, Stokes EA, Wordsworth S, et al. *A multicentre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (TITRe2).* Health Technol Assess 2016, 20(60):1-260. Identified in search update. Stokes EA, Wordsworth S, Bargo D, Pike K, Rogers CA, Brierley RC, et al. *Are lower levels of red blood cell transfusion more cost-effective than liberal levels after cardiac surgery? Findings from the TITRe2 randomised controlled trial.* BMJ Open 2016, 6(8):e011311. **Shehata 2012** Shehata N, Burns LA, Nathan H, Hebert P, Hare GM, Fergusson D, et al. *A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery.* Transfusion 2012, 52(1):91–99. **<u>Systematic reviews</u>** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Lelubre C, Vincent JL, Taccone FS. *Red blood cell transfusion strategies in critically ill patients: lessons from recent randomized clinical studies.* Minerva Anestesiol 2016, 82(9):1010-6. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease.* In peer-review [February 2018]. *Indicates the major publication for the study
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Anne-Catherine Vanhove

PICO 10: RBC transfusion triggers in adult haematological patients

Overview evidence table GRADE software (PICO 10)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <8/12 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
RBC transfusion (units)												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	59	30	-	MD **3.1 RBC units lower** (5.31 lower to 0.89 lower)	⊕⊕◯◯ LOW	IMPORTANT
30-day mortality												
2	randomised trials	not serious	not serious	not serious	very serious [b,c]	none	2/88 (2.3%)	4/61 (6.6%)	**RR 0.37** (0.07 to 1.95)	**41 fewer per 1.000** (from 61 fewer to 62 more)	⊕⊕◯◯ LOW	CRITICAL
Patients received RBC transfusion												
2	randomised trials	not serious	not serious	not serious	very serious [b]	none	85/88 (96.6%)	59/61 (96.7%)	**RR 1.00** (0.95 to 1.05)	**0 fewer per 1.000** (from 48 fewer to 48 more)	⊕⊕◯◯ LOW	CRITICAL
Bleeding events (by grade: 0-1 vs 2-4)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7/8 g/dL)**	**more liberal RBC transfusion triggers (Hb <8/12 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	50/59 (84.7%)	25/30 (83.3%)	**RR 1.02** (0.84 to 1.23)	**17 more per 1.000** (from 133 fewer to 192 more)	⊕⊕◯◯ LOW	IMPORTANT
Length of inpatient stay (days)												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	59	30	-	median **0.5 days lower** (0 to 0)	⊕⊕◯◯ LOW	IMPORTANT
Fatigue scale score												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	59	30	-	median **0.3 points higher** (0 to 0)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Lack of generalizibility: evidence from 1 USA study; b. Limited sample size or low number of events; c. Large variability of results

Detailed evidence summary (PICO 10)

EVIDENCE SUMMARY

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In adult haematological patients (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: **Systematic reviews** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews) **Individual experimental studies** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 thrombocytopeni*:ti OR thrombocytopaeni*:ti OR leukemi*:ti OR leukaemi*:ti OR lymphom*:ti OR "aplastic anemia":ti OR "aplastic anaemia":ti OR myelodysplas*:ti OR myeloproliferat*:ti OR myeloma:ti OR lymphogranulomato*:ti OR histiocy*:ti OR granulom*:ti OR thrombocythemi*:ti OR thrombocythaemi*:ti OR polycythemi*:ti OR polycythaemi*:ti OR myelofibros*:ti OR AML:ti OR CLL:ti OR CML:ti OR Hodgkin*:ti OR burkitt*:ti OR lymphosarcom*:ti OR brill-symmer*:ti OR sezary:ti OR ((haematolog*:ti OR hematolog*:ti OR blood:ti OR red cell*:ti OR white cell*:ti OR marrow:ti OR platelet*:ti) AND (malignan*:ti OR oncolog*:ti OR cancer*:ti OR neoplasm*:ti OR carcinoma*:ti)) OR chemotherap*:ti OR radiotherap*:ti OR chemoradiotherap*:ti

	OR "stem cell":ti OR "stem cells" OR "progenitor cell":ti OR "progenitor cells":ti OR bone marrow transplant*:ti OR bone marrow graft*:ti OR "bone marrow rescue":ti OR rituximab:ti OR antineoplast*:ti OR anti-neoplast*:ti OR ASCT:ti OR ABMT:ti OR PBPC:ti OR PBSCT:ti OR PSCT:ti OR BMT:ti OR SCT:ti OR HSCT:ti OR "haematology patients":ti OR "hematology patients":ti OR "haematological patients":ti OR "hematological patients":ti OR "hemato-oncology patients":ti OR "haemato-oncology patients":ti OR remission:ti OR ((consolidat*:ti OR induct*:ti OR maintenance:ti OR conditioning*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti OR patient*:ti)) OR ((cytosta*:ti OR cytotox*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti)) OR ((multimodal*:ti OR multi-modal*:ti) AND (treat*:ti OR therap*:ti)) OR (combi*:ti AND modalit*:ti) OR (allograft*:ti OR allo-graft*:ti OR allotransplant*:ti OR allo-transplant*:ti OR ((allogen*:ti OR allo-gen*:ti) AND (transplant*:ti OR trasplant*:ti OR graft*:ti OR rescue*)) OR homograft*:ti OR homo-graft*:ti OR homolog*:ti OR homotransplant*:ti OR homo-transplant*:ti OR homotrasplant*:ti OR homo trasplant*:ti) OR (autograft*:ti OR autograft*:ti OR autotransplant*:ti OR auto-transplant*:ti OR mini-transplant*:ti) OR (autolog*:ti AND (transplant*:ti OR graft*:ti OR trasplant*:ti OR rescu*:ti)) #3 #1 AND #2 (results #hits on 13 July 2017: 531 trials) **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy: **<u>Systematic reviews</u>** #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 #6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) #7 #5 AND #6 (Results #hits (on 6 July 2017): 224) **<u>Individual experimental/observational studies</u>** #1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR

	haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 (thrombocytopeni*[TI] OR thrombocytopaeni*[TI] OR leukemi*[TI] OR leukaemi*[TI] OR lymphom*[TI] OR "aplastic anemia"[TI] OR "aplastic anaemia"[TI] OR myelodysplas*[TI] OR myeloproliferat*[TI] OR myeloma[TI] OR lymphogranulomato*[TI] OR histiocy*[TI] OR granulom*[TI] OR thrombocythemi*[TI] OR thrombocythaemi*[TI] OR polycythemi*[TI] OR polycythaemi*[TI] OR myelofibros*[TI] OR AML[TI] OR CLL[TI] OR CML[TI] OR Hodgkin*[TI] OR burkitt*[TI] OR lymphosarcom*[TI] OR brill-symmer*[TI] OR sezary[TI] OR ((haematolog*[TI] OR hematolog*[TI] OR blood[TI] OR red cell*[TI] OR white cell*[TI] OR marrow[TI] OR platelet*[TI]) AND (malignan*[TI] OR oncolog*[TI] OR cancer*[TI] OR neoplasm*[TI] OR carcinoma*[TI])) OR chemotherap*[TI] OR radiotherap*[TI] OR chemoradiotherap*[TI] OR "stem cell"[TI] OR "stem cells" OR "progenitor cell"[TI] OR "progenitor cells"[TI] OR bone marrow transplant*[TI] OR bone marrow graft*[TI] OR "bone marrow rescue"[TI] OR rituximab[TI] OR antineoplast*[TI] OR anti-neoplast*[TI] OR ASCT[TI] OR ABMT[TI] OR PBPC[TI] OR PBSCT[TI] OR PSCT[TI] OR BMT[TI] OR SCT[TI] OR HSCT[TI] OR "haematology patients"[TI] OR "hematology patients"[TI] OR "haematological patients"[TI] OR "hematological patients"[TI] OR "hemato-oncology patients"[TI] OR "haemato-oncology patients"[TI] OR remission[TI] OR ((consolidat*[TI] OR induct*[TI] OR maintenance[TI] OR conditioning*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI] OR patient*[TI])) OR ((cytosta*[TI] OR cytotox*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI])) OR ((multimodal*[TI] OR multi-modal*[TI]) AND (treat*[TI] OR therap*[TI])) OR (combi*[TI] AND modalit*[TI]) OR (allograft*[TI] OR allo-graft*[TI] OR allotransplant*[TI] OR allo-transplant*[TI] OR ((allogen*[TI] OR allo-gen*[TI]) AND (transplant*[TI] OR trasplant*[TI] OR graft*[TI] OR rescue*)) OR homograft*[TI] OR homo-graft*[TI] OR homolog*[TI] OR homotransplant*[TI] OR homo-transplant*[TI] OR homotrasplant*[TI] OR homo trasplant*[TI]) OR (autograft*[TI] OR autograft*[TI] OR autotransplant*[TI] OR auto-transplant*[TI] OR mini-transplant*[TI]) OR (autolog*[TI] AND (transplant*[TI] OR graft*[TI] OR trasplant*[TI] OR rescu*[TI])) #3 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]) #4 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #5 #3 OR #4 #6 #1 AND #2 AND #5 (Results #hits (on 12 July 2017): 1325) **Embase** (via Embase.com interface) using the following search strategy: **<u>Systematic reviews</u>** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti))

	#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 #6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti #7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227) **Individual experimental/observational studies** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 thrombocytopeni*:ti OR thrombocytopaeni*:ti OR leukemi*:ti OR leukaemi*:ti OR lymphom*:ti OR "aplastic anemia":ti OR "aplastic anaemia":ti OR myelodysplas*:ti OR myeloproliferat*:ti OR myeloma:ti OR lymphogranulomato*:ti OR histiocy*:ti OR granulom*:ti OR thrombocythemi*:ti OR thrombocythaemi*:ti OR polycythemi*:ti OR polycythaemi*:ti OR myelofibros*:ti OR AML:ti OR CLL:ti OR CML:ti OR Hodgkin*:ti OR burkitt*:ti OR lymphosarcom*:ti OR brill-symmer*:ti OR sezary:ti OR ((haematolog*:ti OR hematolog*:ti OR blood:ti OR red cell*:ti OR white cell*:ti OR marrow:ti OR platelet*:ti) AND (malignan*:ti OR oncolog*:ti OR cancer*:ti OR neoplasm*:ti OR carcinoma*:ti)) OR chemotherap*:ti OR radiotherap*:ti OR chemoradiotherap*:ti OR "stem cell":ti OR "stem cells" OR "progenitor cell":ti OR "progenitor cells":ti OR bone marrow transplant*:ti OR bone marrow graft*:ti OR "bone marrow rescue":ti OR rituximab:ti OR antineoplast*:ti OR anti-neoplast*:ti OR ASCT:ti OR ABMT:ti OR PBPC:ti OR PBSCT:ti OR PSCT:ti OR BMT:ti OR SCT:ti OR HSCT:ti OR "haematology patients":ti OR "hematology patients":ti OR "haematological patients":ti OR "hematological patients":ti OR "hemato-oncology patients":ti OR "haemato-oncology patients":ti OR remission:ti OR ((consolidat*:ti OR induct*:ti OR maintenance:ti OR conditioning*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti OR patient*:ti)) OR ((cytosta*:ti OR cytotox*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti)) OR ((multimodal*:ti OR multi-modal*:ti) AND (treat*:ti OR therap*:ti)) OR (combi*:ti AND modalit*:ti) OR (allograft*:ti OR allo-graft*:ti OR allotransplant*:ti OR allo-transplant*:ti OR ((allogen*:ti OR allo-gen*:ti) AND (transplant*:ti OR trasplant*:ti OR graft*:ti OR rescue*)) OR homograft*:ti OR homo-graft*:ti OR homolog*:ti OR homotransplant*:ti OR homo-transplant*:ti OR homotrasplant*:ti OR homo trasplant*:ti) OR (autograft*:ti OR autograft*:ti OR autotransplant*:ti OR auto-transplant*:ti OR mini-transplant*:ti) OR (autolog*:ti AND (transplant*:ti OR graft*:ti OR trasplant*:ti OR rescu*:ti)) #3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti) #4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR

	'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp) #5 #3 OR #4 #6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 735) **Transfusion evidence library** **<u>Systematic reviews</u>** #1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs) **<u>Individual experimental studies</u>** #1 Clinical specialty: Haematology and oncology #2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht #3 #1 AND #2 (results #hits on 11 July 2017: 361 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update)
In/Exclusion criteria	**Population:** <u>Included:</u> adult haematological patients, a.) acute malignant haematological diseases like acute lymphatic leukemia (ALL), etc. under different therapeutic regimen: aa.) chemotherapy, ab.) hematopoietic stem cell transplantation; b.) chronic malignant haematological diseases (extremely rare in children) c.) hereditary haematological diseases (typically "benign") associated with anemia like sickle cell disease, thalassemia, etc an increasing problem in Europe! Based on the amount of evidence that will be identified, different subgroups analyses (e.g. sickle cell disease versus thalassemia) will be conducted. <u>Excluded:</u> children, infants or neonates. **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction,

	congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** Included: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
DeZern, 2016, USA	Experimental: RCT	89 acute leukaemia participants (acute myeloid leukaemia, acute lymphoblastic leukaemia/ lymphoma, acute promyelocytic leukaemia, treatment-related myeloid neoplasm, highgrade myelodysplastic syndrome) more than 18 years of age admitted to the inpatient leukaemia services with plans for inpatient myelosuppressive chemotherapy • Restrictive group (n=59): mean age (interquartile range) = 56 (45.5 to 67) years • Liberal group (n=30): mean age (interquartile range) = 62.5 (55.2 to 67.8) years	Restrictive group: single-unit RBC transfusion if Hb <7 g/dL Liberal group: single-unit RBC transfusion if Hb <8 g/dL	The authors have disclosed no COI. This work was supported by a grant from the Society for the Advancement of Blood Management (SABM) sponsored by Haemonetics Corp. (Braintree, MA; to AED).

Webert, 2008, Canada	Experimental: RCT	60 adult participants with acute leukaemia were randomly allocated to 1 of 2 groups: • Restrictive group: n=29; M/F=18/11; mean (SD) age = 50.8 (15.3) years • Liberal group: n=31; M/F = 14/17; mean (SD) age = 45.3 (16.8) years	Restrictive group: 2-unit RBC transfusion if Hb <8 g/dL, with a target range of 8.5 to 9.5 g/dL Liberal group: 2-unit RBC transfusion if Hb <12 g/dL	This study was funded by a grant from Canadian Blood Services and a CIHR Canada Research Chair. KEW was supported by a Canadian Blood Services/Novo Nordisk Research Fellowship in Hemostasis. RJC is a Canada Research Chair.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
PRIMARY OUTCOMES				
RBC transfusions (units)	Restrictive vs liberal	Statistically significant: 8.2±4.2 vs 42.4±5.0 MD: -3.10, 95%CI [-5.31;-0.89] (p=0.006)* (Figure 1) *In favour of restrictive group*	1, 59 vs 30 §	DeZern, 2016
30-day mortality	Restrictive vs liberal	Not statistically significant: 2/88 vs 4/61 § RR: 0.37, 95%CI [0.07;1.95] ¥ (p=0.24)* (Figure 2)	2, 88 vs 61	DeZern, 2016, Webert 2008
Participants exposed to blood transfusion	Restrictive vs liberal	Not statistically significant: 85/88 vs 59/61 § RR: 1.0, 95%CI [0.95;1.05] (p=1.00)* (Figure 3)	2, 88 vs 61	DeZern, 2016, Webert 2008
SECONDARY OUTCOMES				
Bleeding events (by grade: 0-1 vs 2-4)	Restrictive vs liberal	Not statistically significant: 50/59 vs 25/30 § RR: 1.02, 95%CI [0.84;1.23] (p=0.86)* (Figure 4)	1, 59 vs 30	DeZern, 2016
Length of inpatient stay (days)	Restrictive vs liberal	Not statistically significant: 35.5 (31.2-43.8) vs 36.0 (29.2-44.0) (median (interquartile range)) (p=0.53)	1, 59 vs 30 §	DeZern, 2016
Fatigue scale score	Restrictive vs liberal	Not statistically significant: 4.8 (4.0-5.2) vs 4.5 (3.6-5.0) (median (interquartile range)) (p=0.32)	1, 59 vs 30 §	DeZern, 2016

Episodes of neutropenic fever (0-1 vs 2-5)	Restrictive vs liberal	Not statistically significant: 38/59 vs 22/30 § RR: 0.88, 95%CI [0.66;1.17] ¥ (p=0.38)* (Figure 5)	1, 59 vs 30	DeZern, 2016

Mean ± SD (unless otherwise indicated)
CI: confidence interval, RR: relative risk, MD: mean difference
* Calculations (RR or MD, 95% CI and/or p-value) done by the reviewer(s) using Review Manager software
¥ Imprecision (large variability of results)
§ Imprecision (limited sample size or low number of events)

Forest plots

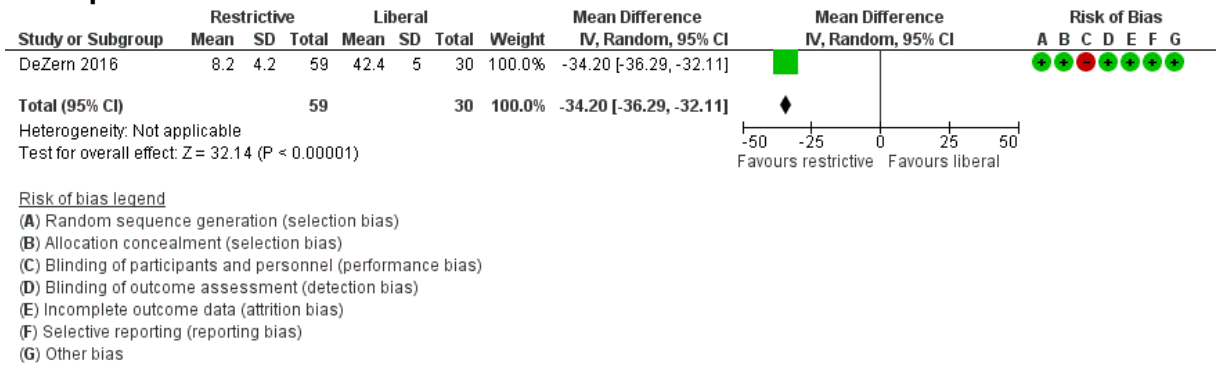


Figure 83: Forest plot of outcome: RBC transfusions (units).

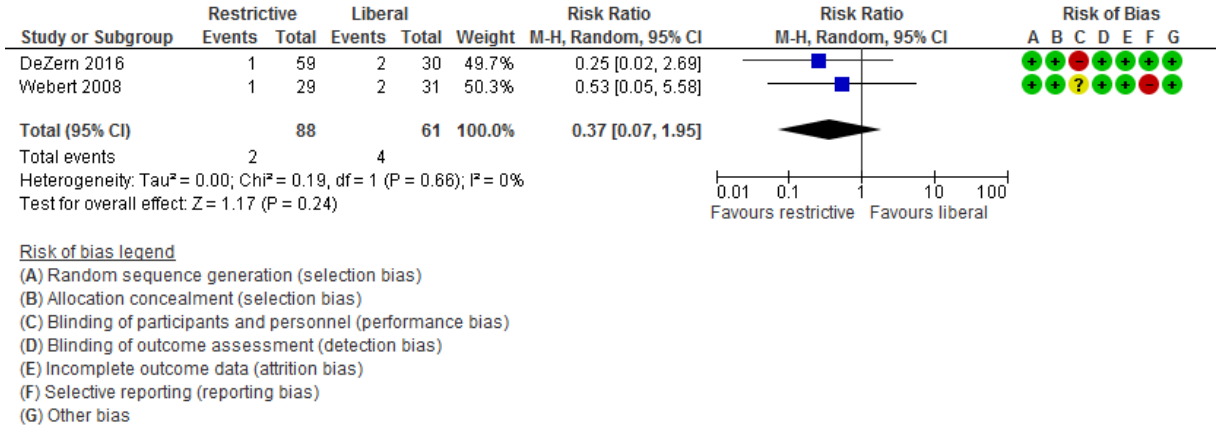


Figure 2: Forest plot of outcome: 30-day mortality

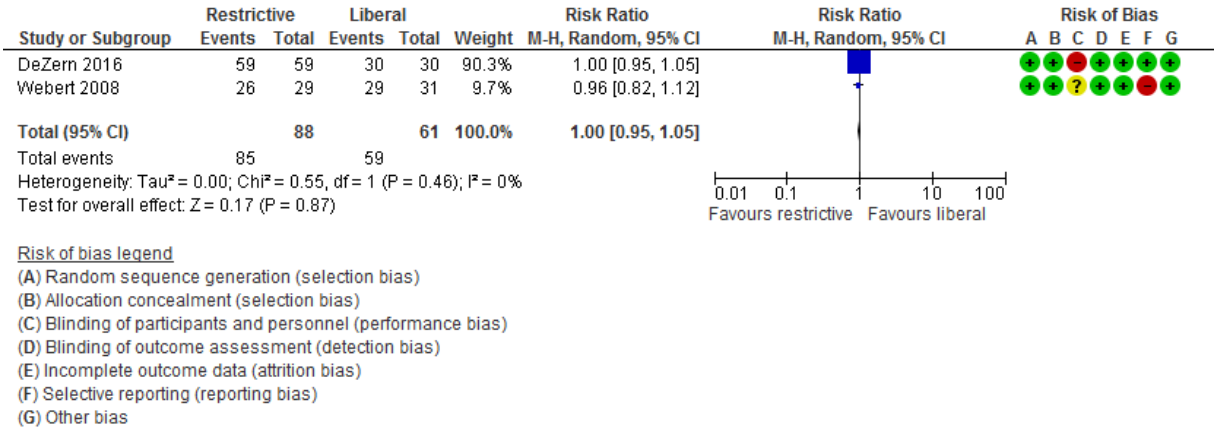


Figure 3: Forest plot of outcome: Participants exposed to blood transfusion

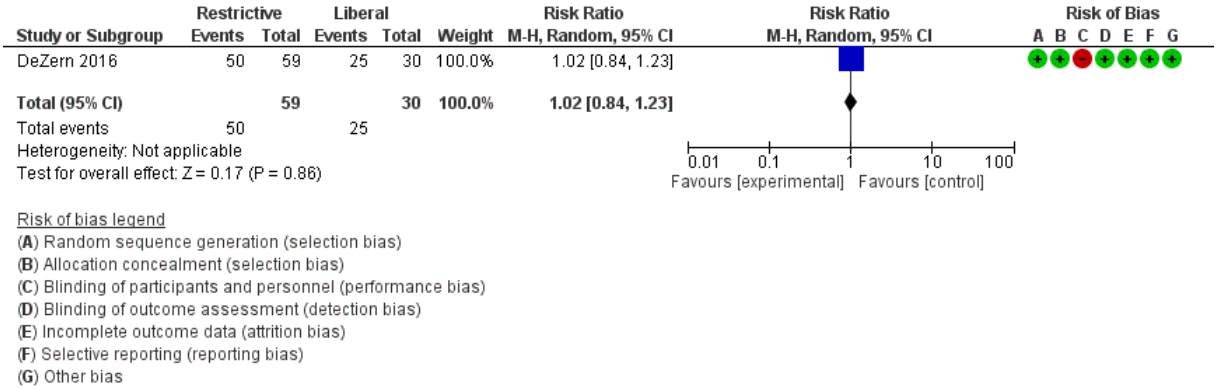


Figure 4: Forest plot of outcome: Bleeding events (by grade: 0-1 vs 2-4)

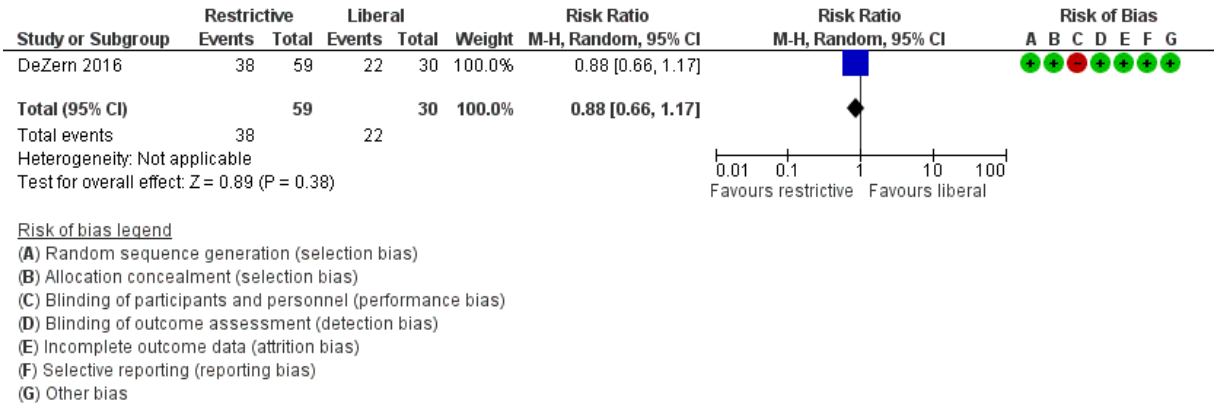


Figure 5: Forest plot of outcome: Episodes of neutropenic fever (0-1 vs 2-5)

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
DeZern, 2016	Randomization: no (computer software generated the random number sequence) Allocation concealment: no (sealed opaque sequentially numbered envelopes were used)	Participants and personnel: yes (participants and personnel were not blinded) Outcome assessors: no (risk varied by outcome: low risk for the outcome of mortality; other secondary outcomes had a high risk)	No	No Pre-registration of study protocol @ ClinicalTrials.Gov (NCT02086773)	No
Webert, 2008	Randomization: no (sequence generation was computer-generated) Allocation concealment: no (allocation was internet-based and central)	Participants and personnel: unclear (participants and personnel were not blinded) Outcome assessors: no (outcomes were assessed blinded)	No (no missing data)	Yes No pre-registration of study protocol	No

Certainty of the body of evidence: see GRADE Evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **DeZern 2016** DeZern AE, Williams K, Zahurak M, Hand W, Stephens RS, King KE, Frank SM, Ness PM. *Red blood cell transfusion triggers in acute leukemia: a randomized pilot study.* Transfusion 2016, 56(7): 1750-1757. **Webert 2008** Webert KE, Cook RJ, Couban S, Carruthers J, Lee KA, Blajchman MA, Lipton JH, Brandwein JM, Heddle NM. *A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation.* Transfusion 2008, 48(1):81–91. **Systematic reviews** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042.

	Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease*. In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel

PICO 11: RBC transfusion triggers in adult patients with solid tumours

Overview evidence table GRADE software (PICO 11)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)**	**more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Patients exposed to RBC transfusions												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	33/101 (32.7%)	47/97 (48.5%)	**RR 0.67** (0.48 to 0.95)	**160 fewer per 1.000** (from 24 fewer to 252 fewer)	⨁⨁◯◯ LOW	IMPORTANT
30-day mortality												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	23/101 (22.8%)	8/97 (8.2%)	**RR 2.76** (1.30 to 5.87)	**145 more per 1.000** (from 25 more to 402 more)	⨁◯◯◯ VERY LOW	CRITICAL
Renal failure												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	44/101 (43.6%)	45/97 (46.4%)	**RR 0.94** (0.69 to 1.28)	**28 fewer per 1.000** (from 130 more to 144 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Myocardial infarction												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)**	**more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	1/101 (1.0%)	0/97 (0.0%)	**RR 1.17** (0.33 to 4.10)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Congestive heart failure												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	5/101 (5.0%)	2/97 (2.1%)	**RR 2.40** (0.48 to 12.08)	**29 more per 1.000** (from 11 fewer to 228 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Cardiac events												
1	randomised trials	not serious	not serious	serious [a]	serious [c]	none	14/101 (13.9%)	5/97 (5.2%)	**RR 2.69** (1.01 to 7.18)	**87 more per 1.000** (from 1 more to 319 more)	⊕⊕◯◯ LOW	CRITICAL
CVA-stroke												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	3/101 (3.0%)	0/97 (0.0%)	**RR 6.73** (0.35 to 128.52)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)**	**more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Sepsis-bacteraemia												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	22/101 (21.8%)	7/97 (7.2%)	**RR 1.10** (0.41 to 2.91)	**7 more per 1.000** (from 43 fewer to 138 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Pneumonia												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	8/101 (7.9%)	13/97 (13.4%)	**RR 1.63** (0.87 to 3.04)	**84 more per 1.000** (from 17 fewer to 273 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Pneumonia or wound infection												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	31/101 (30.7%)	21/97 (21.6%)	**RR 1.42** (0.88 to 2.29)	**91 more per 1.000** (from 26 fewer to 279 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Thromboembolism												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)**	**more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	1/101 (1.0%)	1/97 (1.0%)	**RR 0.96** (0.06 to 15.47)	**0 fewer per 1.000** (from 10 fewer to 149 more)	⨁◯◯◯ VERY LOW	CRITICAL
Transfusion-related hemolysis (acute or delayed)												
1	randomised trials	not serious	not serious	serious [d]	very serious [c]	none	0/44 (0.0%)	0/43 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
Transfusion-related fever												
1	randomised trials	not serious	not serious	serious [d]	very serious [c]	none	8/44 (18.2%)	10/43 (23.3%)	**RR 0.78** (0.34 to 1.79)	**51 fewer per 1.000** (from 153 fewer to 184 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Transfusion-related pulmonary edema												
1	randomised trials	not serious	not serious	serious [d]	very serious [c]	none	0/44 (0.0%)	2/43 (4.7%)	**RR 0.20** (0.01 to 3.96)	**37 fewer per 1.000** (from 46 fewer to 138 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Transfusion-related new alloantibodies												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7/9.7/10 g/dL)**	**more liberal RBC transfusion triggers (Hb <9/11.5/12 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [d]	very serious [c]	none	2/44 (4.5%)	1/43 (2.3%)	**RR 1.95** (0.18 to 20.77)	**22 more per 1.000** (from 19 fewer to 460 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Complications from RBC transfusions												
1	randomised trials	not serious	not serious	serious [e]	very serious [c]	none	0/65 (0.0%)	0/68 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Lack of generalizibility: evidence from 1 Brazilian (feasibility) study; b. Limited sample size/low number of events; c. Limited sample size, low number of events and/or large variability of results; d. Lack of generalizibility: evidence from 1 South Korean study; e. Lack of generalizibility: evidence from 1 Danish study

Detailed evidence summary (PICO 11)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In adult patients with solid tumours (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. <u>Databases</u> **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: **<u>Systematic reviews</u>** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews) **<u>Individual experimental studies</u>** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 neoplas*:ti OR tumor*:ti OR tumour*:ti OR Krebsti OR cancer*ti OR malignan*ti OR carcino*ti OR karzino*ti OR sarcom*ti OR leukaem*ti OR leukam*ti OR leuc*ti OR lymphom*ti OR melano*ti OR metastas*ti OR mesothelio*ti OR mesotelio*ti OR carcinomatous*ti OR gliom*ti OR glioblastom*ti OR osteo*sarcom*ti OR blastom*ti OR neuroblastom*ti OR adenocarcinoma*ti OR choriocarcinoma*ti OR teratoma*ti #3 #1 AND #2 (results #hits on 13 July 2017: 36 trials) **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

	Systematic reviews #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 #6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) #7 #5 AND #6 (Results #hits (on 6 July 2017): 224) **Individual experimental/observational studies** #1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 "Neoplasms by histologic type"[Mesh] OR "Neoplasms by site"[Mesh] OR neoplas*[TI] OR tumor*[TI] OR tumour*[TI] OR Krebs[TI] OR cancer*[TI] OR malignan*[TI] OR carcino*[TI] OR karzino*[TI] OR sarcom*[TI] OR leukaem*[TI] OR leukam*[TI] OR leuc*[TI] OR lymphom*[TI] OR melano*[TI] OR metastas*[TI] OR mesothelio*[TI] OR mesotelio*[TI] OR carcinomatous*[TI] OR gliom*[TI] OR glioblastom*[TI] OR osteo*sarcom*[TI] OR blastom*[TI] OR neuroblastom*[TI] OR adenocarcinoma*[TI] OR choriocarcinoma*[TI] OR teratoma*[TI] #3 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]) #4 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #5 #3 AND #4 #6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 1315)

	Embase (via Embase.com interface) using the following search strategy: **Systematic reviews** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 #6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti #7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227) **Individual experimental/observational studies** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 neoplas*:ti OR tumor*:ti OR tumour*:ti OR Krebsti OR cancer*ti OR malignan*ti OR carcino*ti OR karzino*ti OR sarcom*ti OR leukaem*ti OR leukam*ti OR leuc*ti OR lymphom*ti OR melano*ti OR metastas*ti OR mesothelio*ti OR mesotelio*ti OR carcinomatous*ti OR gliom*ti OR glioblastom*ti OR osteo*sarcom*ti OR blastom*ti OR neuroblastom*ti OR adenocarcinoma*ti OR choriocarcinoma*ti OR teratoma*ti #3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti) #4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp) #5 #3 OR #4 #6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 735) **Transfusion evidence library**

	Systematic reviews #1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs) **Individual experimental studies** #1 Clinical specialty: Haematology and oncology #2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht #3 #1 AND #2 (results #hits on 11 July 2017: 361 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: aa: chemotherapy ab: surgery ac: radiotherapy; ad: combinations of aa to ac **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). Exclude: QoL **Study design:** Included: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic

	or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
De Almeida, 2015, Brazil	Experimental: RCT	198 adult participants who underwent a major surgical procedure for abdominal cancer and required postoperative care in the ICU • Liberal: n = 97; mean age (SD) = 64 (14) years • Restrictive: n = 101; mean age (SD) = 64 (12) years	Restrictive group: RBC transfusion if Hb <7 g/dL Liberal group: RBC transfusion if Hb <9 g/dL	The authors have disclosed no COI. Support was provided solely from institutional and/or departmental sources.
Park, 2008, South Korea	Experimental: RCT	87 adult patients with a confirmed diagnosis of measurable advanced gastric cancer and scheduled to receive 5-fluorouracil-based first-line chemotherapy for metastatic/recurrent disease • Liberal: n = 43; median age (interquartile range) = 61 (32-75) years • Restrictive: n = 44; median age (interquartile range) = 55 (28-74) years	Restrictive group: RBC transfusion if Hb <10 g/dL Liberal group: RBC transfusion if Hb <12 g/dL	This study was financially supported by an unrestricted research grant from Gachon University Gil Medical Center, Incheon, South Korea.
Yakymenko, 2017, Denmark	Experimental: RCT	133 patients, 18 years of age or older, with a confirmed diagnosis of malignant solid tumour and planned treatment with chemotherapy • Liberal: n = 68; mean age (SD) = 65 (9.7) years • Restrictive: n = 65; mean age (SD) = 65 (9.9) years	Restrictive group: RBC transfusion if Hb <9.7 g/dL Liberal group: RBC transfusion if Hb <11.5 g/dL (females) or <13.1 g/dL (males)	The authors have disclosed no COI.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
PRIMARY OUTCOMES				
Patients exposed to RBC transfusions	Restrictive vs liberal	Statistically significant: 33/101 vs 47/97 RR: 0.67, 95%CI [0.48;0.95] (p<0.03)* *In favour of restrictive group*	1, 101 vs 97 §	de Almeida, 2015
Median number of RBC transfused	Restrictive vs liberal	Not statistically significant: 2 (median), [1-2, range] vs 2 (median), [1-5, range] (p=0.26)	1, 65 vs 68 §	Yakymenko, 2017
Mortality at 30 days	Restrictive vs liberal	Not statistically significant 23/101 vs 8/97 RR: 2.76, 95%CI [1.30;5.87] (p=0.008)*	1, 101 vs 97 §	de Almeida 2015
SECONDARY OUTCOMES				
Renal failure	Restrictive vs liberal	Not statistically significant 44/101 vs 45/97 RR: 0.94, 95%CI [0.69;1.28] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Myocardial infarction	Restrictive vs liberal	Not statistically significant 1/101vs 0/97 RR: 2.88, 95%CI [0.12;69.91] ¥ (p=0.52)*	1, 101 vs 97 §	de Almeida 2015
Congestive heart failure	Restrictive vs liberal	Not statistically significant 5/101 vs 2/97 RR: 2.40, 95%CI [0.48;12.08] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Cardiac events	Restrictive vs liberal	Not statistically significant 14/101 vs 5/97 RR: 2.69, 95%CI [1.01;7.18] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
CVA-stroke	Restrictive vs liberal	Not statistically significant 3/101 vs 0/97 RR: 6.73, 95%CI [0.35;128.52] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Sepsis - bacteraemia	Restrictive vs liberal	Not statistically significant 22/101 vs 7/97 RR: 1.10, 95%CI [0.41;2.91] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Pneumonia	Restrictive vs liberal	Not statistically significant 8/101 vs 13/97 RR: 1.63, 95%CI [0.87;3.04] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Pneumonia or wound infection	Restrictive vs liberal	Not statistically significant 31/101 vs 21/97 RR: 1.42, 95%CI [0.88;2.29] ¥ (p>0.05)	1, 101 vs 97 §	de Almeida 2015
Thromboembolism	Restrictive vs liberal	Not statistically significant 1/101 vs 1/97	1, 101 vs 97 §	de Almeida 2015

		RR: 0.96, 95%CI [0.06;15.47] ¥ (p>0.05)		
Transfusion-related hemolysis (acute or delayed)	Restrictive vs liberal	Not statistically significant 0/44 vs 0/43 RR: not estimable (p>0.05)*	1, 44 vs 43 §	Park 2008
Transfusion-related fever	Restrictive vs liberal	Not statistically significant 8/44 vs 10/43 RR: 0.78, 95%CI [0.34;1.79] ¥ (p=0.56)*	1, 44 vs 43 §	Park 2008
Transfusion-related allergy with urticaria	Restrictive vs liberal	Not statistically significant 8/44 vs 9/43 RR: 0.87, 95%CI [0.37;2.04] ¥ (p=0.75)*	1, 44 vs 43 §	Park 2008
Transfusion-related pulmonary edema (acute)	Restrictive vs liberal	Not statistically significant 0/44 vs 2/43 RR: 0.20, 95%CI [0.01;3.96] ¥ (p=0.28)*	1, 44 vs 43 §	Park 2008
Transfusion-related viral infection	Restrictive vs liberal	Not statistically significant 0/44 vs 0/43 RR: not estimable (p>0.05)*	1, 44 vs 43 §	Park 2008
Transfusion-related new alloantibodies	Restrictive vs liberal	Not statistically significant 2/44 vs 1/43 RR: 1.95, 95%CI [0.18;20.77] ¥ (p=0.58)*	1, 44 vs 43 §	Park 2008
Number of chemotherapy cycles	Restrictive vs liberal	Not statistically significant 4 (median) [0-9, range] vs 5 (median) [1-12, range] (p=0.537)*	1, 44 vs 43 §	Park 2008
Duration of chemotherapy (months)	Restrictive vs liberal	Not statistically significant 3.8 (median) [IQR not reported] vs 4.1 (median) [IQR not reported] (p=0.773)*	1, 44 vs 43 §	Park 2008
Chemotherapy-related neutropenia	Restrictive vs liberal	Not statistically significant 28/44 vs 23/43 RR: 1.19, 95%CI [0.83;1.70] ¥ (p=0.34)*	1, 44 vs 43 §	Park 2008
Chemotherapy-related neutropenic infection	Restrictive vs liberal	Not statistically significant 7/44 vs 8/43 RR: 0.86, 95%CI [0.34;2.15] ¥ (p=0.74)*	1, 44 vs 43 §	Park 2008
Chemotherapy-related thrombocytopenia	Restrictive vs liberal	Not statistically significant 10/44 vs 11/43 RR: 0.89, 95%CI [0.42;1.87] ¥ (p=0.76)*	1, 44 vs 43 §	Park 2008
Chemotherapy-related fatigue	Restrictive vs liberal	Not statistically significant 11/44 vs 9/43 RR: 1.19, 95%CI [0.55;2.59] ¥ (p=0.65)*	1, 44 vs 43 §	Park 2008

Chemotherapy-related nausea and vomiting	Restrictive vs liberal	Not statistically significant 25/44 vs 23/43 RR: 1.06, 95%CI [0.73;1.55] ¥ (p=0.75)*	1, 44 vs 43 §	Park 2008
Chemotherapy-related oral mucositis	Restrictive vs liberal	Not statistically significant 12/44 vs 16/43 RR: 0.73, 95%CI [0.39;1.36] ¥ (p=0.32)*	1, 44 vs 43 §	Park 2008
Chemotherapy-related diarrhea	Restrictive vs liberal	Not statistically significant 13/44 vs 14/43 RR: 0.91, 95%CI [0.48;1.70] ¥ (p=0.76)*	1, 44 vs 43 §	Park 2008
Chemotherapy-related constipation	Restrictive vs liberal	Not statistically significant 11/44 vs 9/43 RR: 1.19, 95%CI [0.55;2.59] ¥ (p=0.65)*	1, 44 vs 43 §	Park 2008
Complications from RBC transfusions	Restrictive vs liberal	Not statistically significant 0/65 vs 0/68 RR: not estimable	1, 65 vs 68 §	Yakymenko, 2017

Mean ± SD (unless otherwise indicated)

CI: confidence interval, RR: relative risk, MD: mean difference

* Calculations (RR or MD, 95% CI and/or p-value) done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

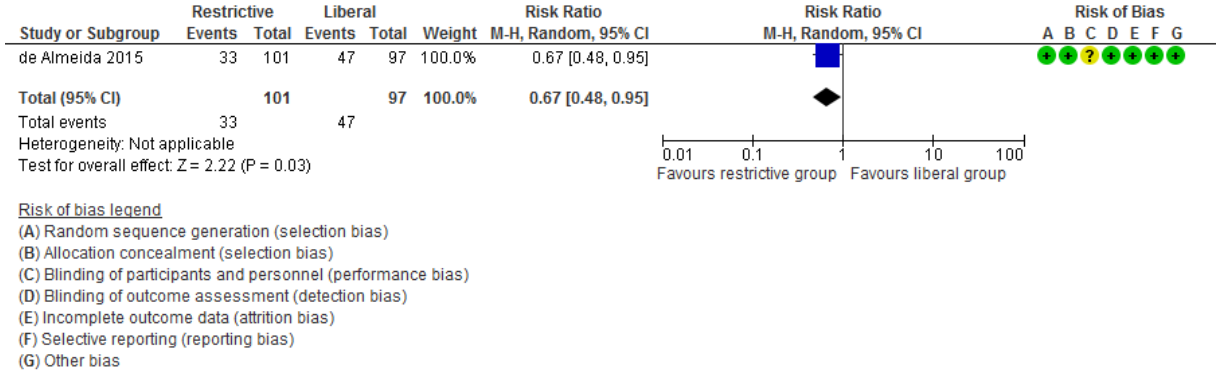


Figure 84: Forest plot of outcome: patients exposed to RBC transfusions

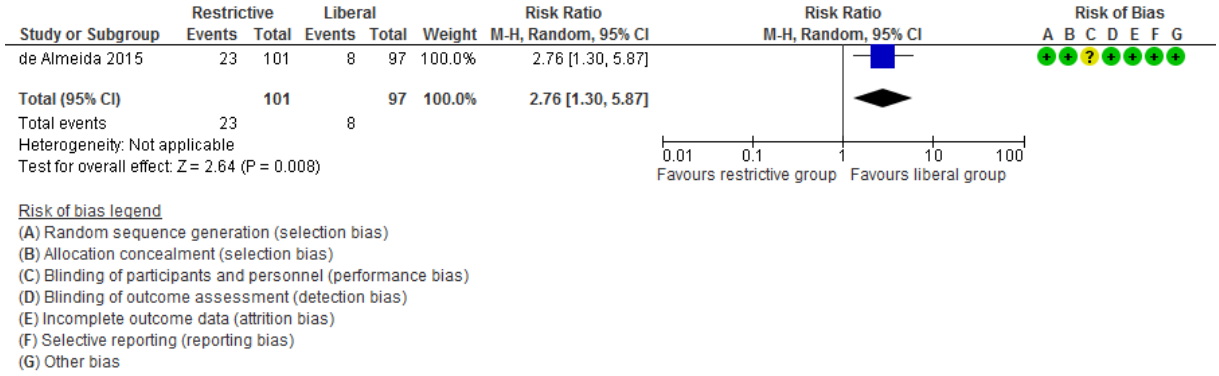


Figure 2: Forest plot of outcome: 30-day mortality

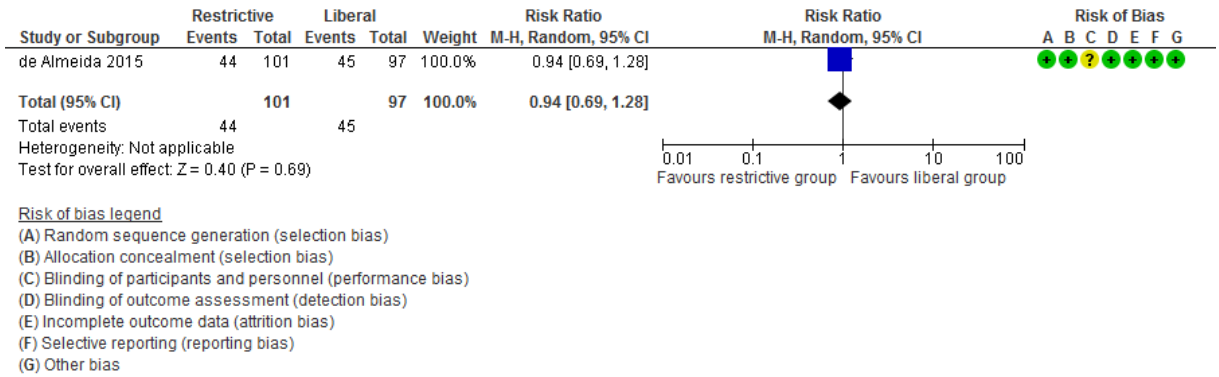
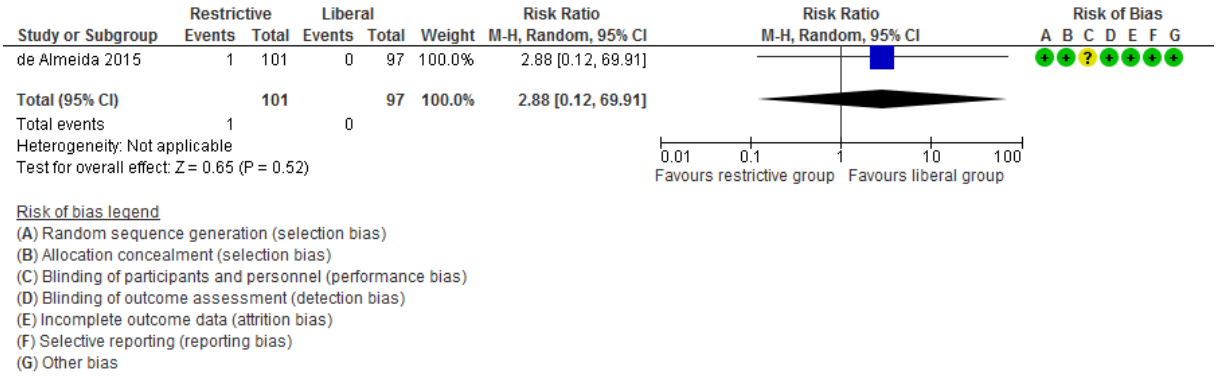
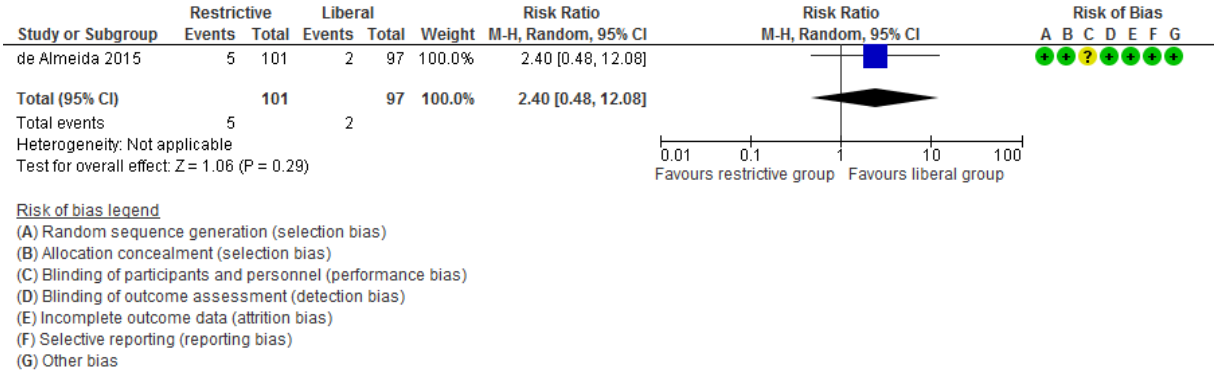


Figure 3: Forest plot of outcome: Renal failure



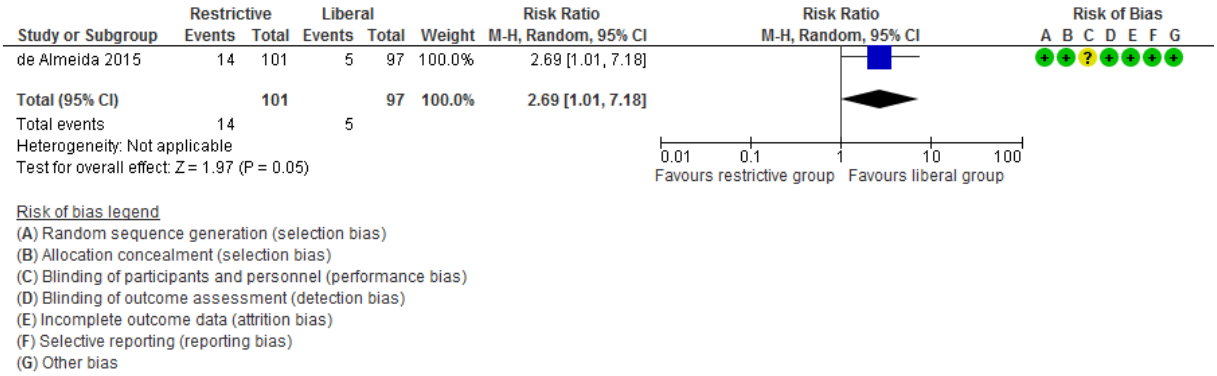
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4: Forest plot of outcome: Myocardial infarction



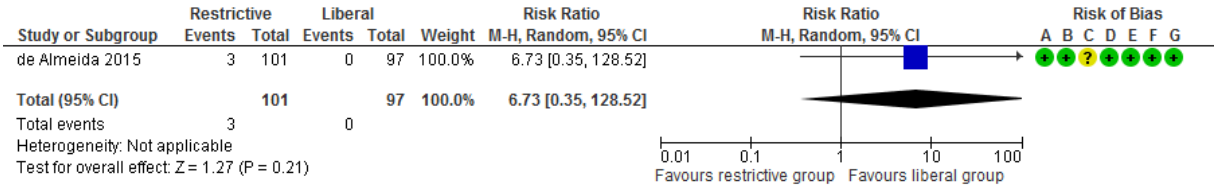
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 5: Forest plot of outcome: Congestive heart failure



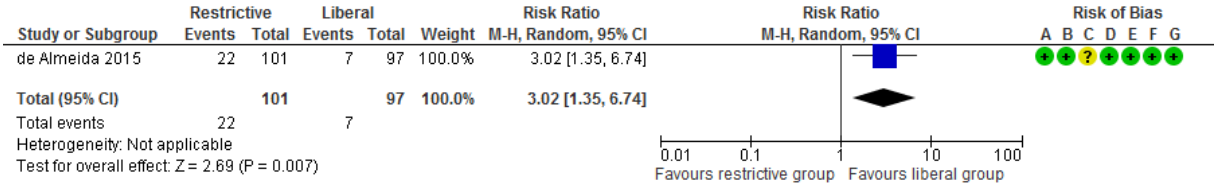
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 6: Forest plot of outcome: Cardiac events



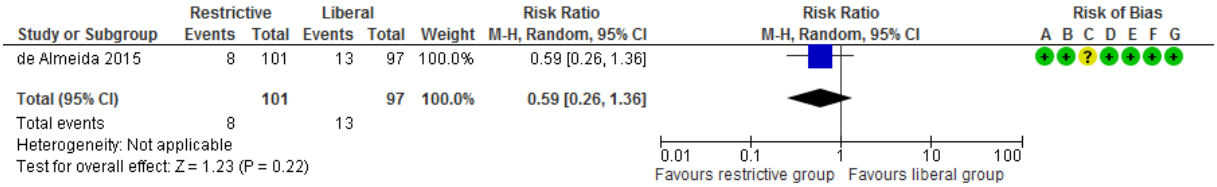
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 7: Forest plot of outcome: CVA-stroke



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 8: Forest plot of outcome: Sepsis-bacteraemia



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 9: Forest plot of outcome: Pneumonia

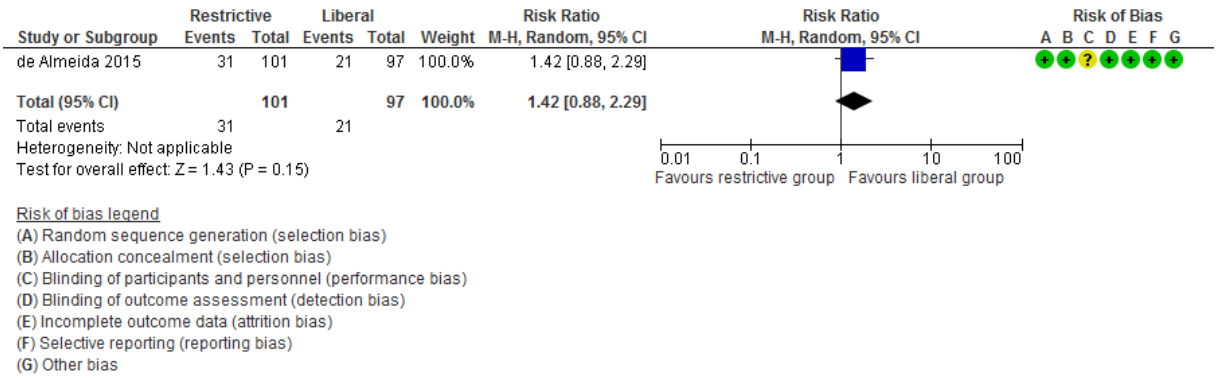


Figure 850: Forest plot of outcome: Pneumonia or wound infection

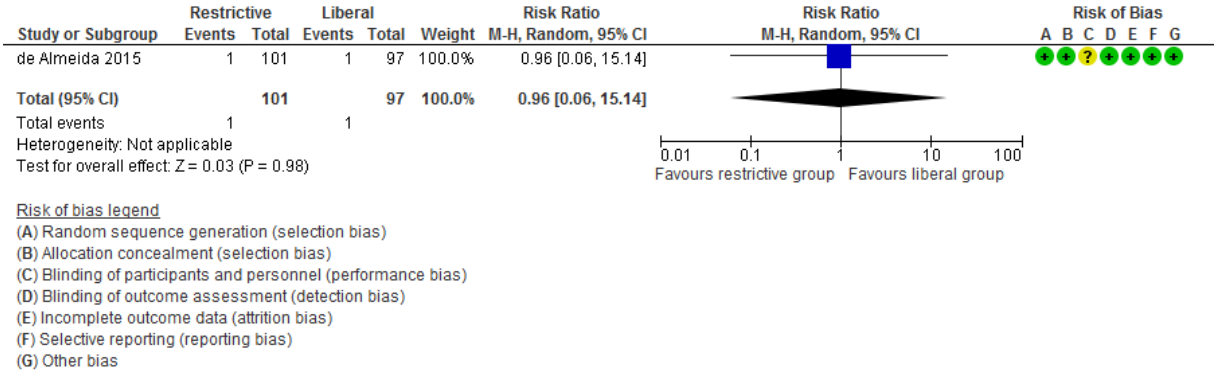
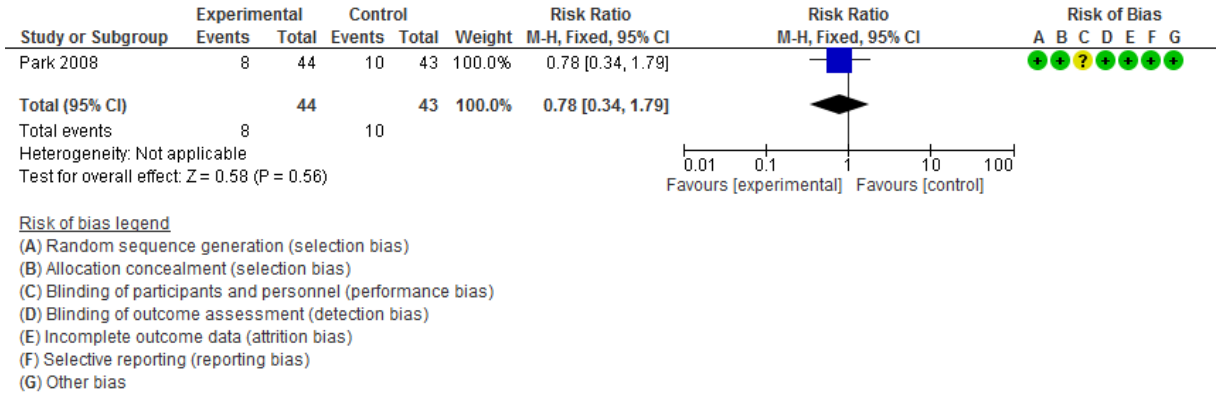


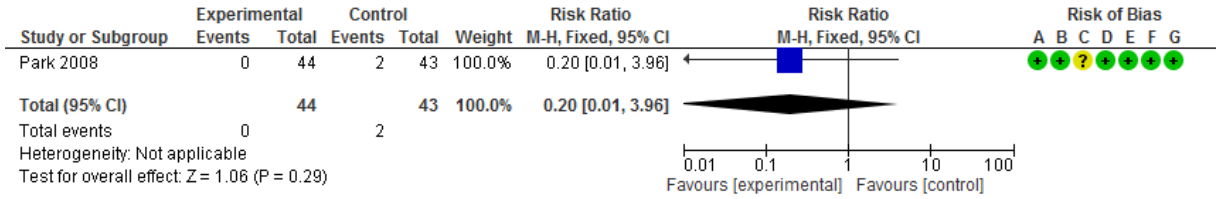
Figure 861: Forest plot of outcome: Thromboembolism

Figure 872: Forest plot of outcome: Transfusion-related hemolysis (acute or delayed)



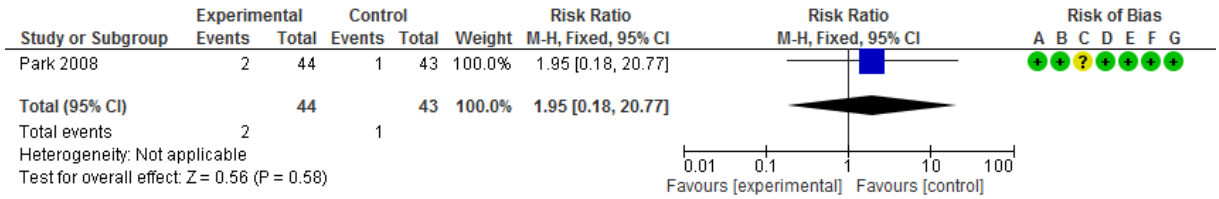
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 883: Forest plot of outcome: Transfusion-related fever



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 894: Forest plot of outcome: Transfusion-related edema



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 905: Forest plot of outcome: Transfusion-related new alloantibodies

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
de Almeida, 2015	Randomization: no (the chief statistician ensured random sequence generation) Allocation concealment: no (the trial used opaque envelopes that were opened sequentially)	Personnel and participants: unclear (clinicians or participants were not blinded) Outcome assessment: no (the participants and the study investigators who classified outcomes and those who conducted the follow-up telephone assessments were blinded to the study-group assignments and had no access to transfusion data	No	No Pre-registration of study protocol @ ClinicalTrials.gov (NCT01502215)	No
Park, 2008	Randomization: no Allocation concealment: no (The random allocation sequence was generated by a table made from the permuted block method. A permuted block size of four was used but there was no stratification.)	Personnel and participants: unclear Outcome assessment: no (an independent investigator was blinded to the study results)	No	Yes No pre-registration of study protocol	No
Yakymenko, 2017	Randomization: no (computer	Personnel and participants:	No (all analyses were performed	No	No

	program was used) Allocation concealment: unclear	Outcome assessment:	according to the intention-to-treat principles)	Pre-registration of study protocol @ ClinicalTrials.gov (NCT01116479)	

Certainty of the body of evidence: see GRADE Evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **de Almeida 2015** de Almeida JP, Vincent JL, Galas FR, de Almeida EP, Fukushima JT, Osawa EA, Bergamin F, Park CL, Nakamura RE, Fonseca SM, Cutait G, Alves JI, Bazan M, Vieira S, Sandrini AC, Palomba H, Ribeiro U Jr, Crippa A, Dalloglio M, Diz Mdel P, Kalil Filho R, Auler JO Jr, Rhodes A, Hajjar LA. *Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial*. Anesthesiology. 2015, 122(1):29-38. **Park 2008** Park SH, Nam E, Bang SM, Cho EK, Shin DB, Lee JH. *A randomized trial of anemia correction with two different hemoglobin targets in the first-line chemotherapy of advanced gastric cancer*. Cancer Chemother Pharmacol. 2008, 62(1):1-9. **Yakymenko 2017** Yakymenko D, Frandsen KB, Christensen IJ, Norgaard A, Johansson PI, Daugaard G, Mau-Sorensen M. *Randomised feasibility study of a more liberal haemoglobin trigger for red blood cell transfusion compared to standard practice in anaemic cancer patients treated with chemotherapy*. Transfus Med. 2017 Jun 29. **Systematic reviews** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease.* In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel

PICO 12: RBC transfusion triggers in adult patients with acute central nervous system injury

Overview evidence table GRADE software (PICO 12)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospital mortality												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	49/586 (8.4%)	101/979 (10.3%)	**RR 0.81** (0.59 to 1.12)	**20 fewer per 1.000** (from 12 more to 42 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital mortality (patients with GCS ≤8)												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	24/110 (21.8%)	56/177 (31.6%)	**RR 0.69** (0.46 to 1.04)	**98 fewer per 1.000** (from 13 more to 171 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Patients with GCS score ≤8 that received RBC transfusion												
1	observational studies	not serious	not serious	serious [a]	not serious	none	47/112 (42.0%)	112/203 (55.2%)	**RR 0.76** (0.59 to 0.98)	**132 fewer per 1.000** (from 11 fewer to 226 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
ICU length of stay												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	not serious	none	586	979	-	MD **1.2 days more** (2.13 more to 4.53 more)	⊕◯◯◯ VERY LOW	IMPORTANT
ICU length of stay in patients with GCS score ≤8												
1	observational studies	not serious	not serious	serious [a]	not serious	none	112	203	-	MD **0.7 days more** (2.07 more to 3.47 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Days requiring mechanical ventilation												
1	observational studies	not serious	not serious	serious [a]	not serious	none	586	979	-	MD **0.8 days fewer** (3.19 fewer to 1.59 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Days requiring mechanical ventilation in patients with GCS score ≤8												
1	observational studies	not serious	not serious	serious [a]	not serious	none	112	203	-	MD **1 days fewer** (3.2 fewer to 1.2 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Days with fever												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	Statistically significant in favour of restrictive transfusion trigger (p=0.01)				⊕◯◯◯ VERY LOW	NOT IMPORTANT
Days with fever in patients with GCS ≤8												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	112	203	-	MD **0.2 days fewer** (0.75 fewer to 0.35 more)	⊕◯◯◯ VERY LOW	NOT IMPORTANT
ARDS/ALI												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	7/561 (1.2%)	22/848 (2.6%)	**RR 0.48** (0.21 to 1.12)	**13 fewer per 1.000** (from 3 more to 20 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
ARDS/ALI in patients with GCS ≤8												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	5/110 (4.5%)	15/177 (8.5%)	**RR 0.54** (0.20 to 1.43)	**39 fewer per 1.000** (from 36 more to 68 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
DVT/PE												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	38/561 (6.8%)	46/848 (5.4%)	**RR 1.25** (0.82 to 1.89)	**14 more per 1.000** (from 10 fewer to 48 more)	⨁◯◯◯ VERY LOW	CRITICAL
DVT/PE in patients with GCS ≤8												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	13/110 (11.8%)	18/177 (10.2%)	**RR 1.16** (0.59 to 2.28)	**16 more per 1.000** (from 42 fewer to 130 more)	⨁◯◯◯ VERY LOW	CRITICAL
30-day/60-day/hospital mortality												
1	randomised trials	not serious	not serious	serious [c]	very serious [b]	none	5/29 (17.2%)	5/38 (13.2%)	**RR 1.31** (0.42 to 4.10)	**41 more per 1.000** (from 76 fewer to 408 more)	⨁◯◯◯ VERY LOW	CRITICAL
Number of RBC transfusions (units per patient)												
1	randomised trials	serious [d]	not serious	serious [c]	serious [b]	none	29	38	-	MD **3.2 units per patient lower** (4.33 lower to 2.07 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb <7 g/dL)**	**more liberal RBC transfusion triggers (Hb <10 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Proportion transfused												
1	randomised trials	serious [d]	not serious	serious [c]	serious [b]	none	17/29 (58.6%)	38/38 (100.0%)	**RR 0.59** (0.44 to 0.80)	**410 fewer per 1.000** (from 200 fewer to 560 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Multiple organ dysfunction												
1	randomised trials	not serious	not serious	serious [c]	very serious [b]	none	29	38	-	MD **0.7 higher** (1.07 lower to 2.47 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Proportion who developed infection												
1	randomised trials	not serious	not serious	serious [c]	very serious [b]	none	2/29 (6.9%)	2/38 (5.3%)	**RR 1.31** (0.20 to 8.76)	**16 more per 1.000** (from 42 fewer to 408 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Lack of generalizibility: evidence from 1 USA study; b. Large variability in results and/or low number of events or lack of data; c. Lack of generalizibility: evidence from 1 Canadian study; d. Detection bias

Detailed evidence summary (PICO 12)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with acute central nervous system (CNS) injury (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: **Systematic reviews** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews) **Individual experimental studies** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 [mh "Central Nervous System Diseases"] #3 (Disease*:ti,ab OR disorder*:ti,ab OR injury:ti,ab OR injuries:ti,ab) AND (brain:ti,ab OR "spinal cord":ti,ab OR "central nervous system":ti,ab OR CNS:ti,ab) #4 #2 OR #3 #5 #1 AND #4 (results #hits on 13 July 2017: 205 trials **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy: **Systematic reviews**

	#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 #6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) #7 #5 AND #6 (Results #hits (on 6 July 2017): 224) **<u>Individual experimental/observational studies</u>** #1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 "Central Nervous System Diseases"[Mesh] #3 (Disease*[TIAB] OR disorder*[TIAB] OR injury[TIAB] OR injuries[TIAB]) AND (brain[TIAB] OR "spinal cord"[TIAB] OR "central nervous system"[TIAB] OR CNS[TIAB]) #4 #2 OR #3 #5 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]) #6 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #7 #5 AND #6 #8 #1 AND #4 AND #7 (Results #hits (on 13 July 2017): 743) **Embase** (via Embase.com interface) using the following search strategy: **<u>Systematic reviews</u>**

	#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 #6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti #7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227) **<u>Individual experimental/observational studies</u>** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 (Disease*:ab,ti OR disorder*:ab,ti OR injury:ab,ti OR injuries:ab,ti) AND (brain:ab,ti OR "spinal cord":ab,ti OR "central nervous system":ab,ti OR CNS) #3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti) #4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp) #5 #3 OR #4 #6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 781) **Transfusion evidence library** **<u>Systematic reviews</u>** #1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR

	intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs) **<u>Individual experimental studies</u>** #1 Clinical specialty: Medicine – Neurological disorders #2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht #3 #1 AND #2 (results #hits on 13 July 2017: 11 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** <u>Included:</u> aa. traumatic brain injury; ab. Traumatic injury of the spinal cord; ac. Increase in intracranial pressure **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** <u>Included:</u> The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive

	transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
McIntyre, 2006, Canada	Experimental: randomized controlled trial	67 multiple trauma patients with a closed head injury • Restrictive group (n=29): age = 41.7±20.4 years • Liberal group (n=38): age = 39.8±18.1 years	Restrictive group: single-unit RBC transfusion if Hb <7 g/dL Liberal group: single-unit RBC transfusion if Hb <10 g/dL	Subgroup analysis of the TRICC trial (Hebert 2001 and Wu 2001)
Ngwenya, 2017, USA	Observational: cohort study (retrospective)	1565 consecutive patients with a diagnosis of TBI who were admitted to the intensive care unit (ICU) at San Francisco General Hospital (SFGH) between January 2011 and September 2015. Patients <16 years of age and those who died within 24 hours of admission were excluded: restrictive group (n=586): mean age: 55.0±21.5 years liberal group (n=979): mean age: 52.4±21.8 years	Restrictive RBC transfusion trigger: Hb <7 g/dL Liberal RBC transfusion trigger: Hb <10 g/dL	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
PRIMARY OUTCOMES				
30-day mortality	Restrictive vs liberal	Not statistically significant: 5/29 vs 5/38 § RR: 1.31 [95%CI: 0.42;4.10] ¥ (p=0.64)* (Figure 1)	1, 29 vs 38	McIntyre, 2006
60-day mortality	Restrictive vs liberal	Not statistically significant: 5/29 vs 5/38 § RR: 1.31 [95%CI: 0.42;4.10] ¥ (p=0.64)* (Figure 2)	1, 29 vs 38	McIntyre, 2006

Hospital mortality	Restrictive vs liberal	Not statistically significant: 5/29 vs 5/38 § RR: 1.31 [95%CI: 0.42;4.10] ¥ (p=0.64)* (Figure 3)	1, 29 vs 38	McIntyre, 2006
Hospital mortality (all patients)	Restrictive vs liberal	Not statistically significant: 49/586 vs 101/979 RR: 0.81 [95%CI: 0.59;1.12] ¥ (p=0.21)* (Figure 4)	1, 586 vs 979	Ngwenya, 2017
Hospital mortality (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 24/110 vs 56/177 § RR: 0.69 [95%CI: 0.46;1.04] ¥ (p=0.08)* (Figure 5)	1, 110 vs 177	Ngwenya, 2017
Number of RBC transfusions (units per patient)	Restrictive vs liberal	Statistically significant: 1.4±2.2 vs 4.6±2.5 MD: -3.20 (95%CI: -4.33;-2.07] (p<0.00001)* (Figure 6) *In favour of a restrictive transfusion trigger*	1, 29 vs 38 §	McIntyre, 2006
Proportion transfused	Restrictive vs liberal	Statistically significant: 17/29 vs 38/38 § RR: 0.59 [95%CI: 0.44;0.80] ¥ (p=0.0007)* (Figure 7)	1, 29 vs 38	McIntyre, 2006
Patients with GCS score ≤8 that received RBC transfusion	Restrictive vs liberal	Statistically significant: 47/112 vs 112/203 RR: 0.76 [95%CI: 0.59;0.98] (p=0.03)* (Figure 8) *In favour of a restrictive transfusion trigger*	1, 112 vs 203	Ngwenya, 2017
SECONDARY OUTCOMES				
ICU (days) median and IQ range	Restrictive vs liberal	Not statistically significant: 10 (5-21) vs 8 (5-11) Median difference 2 (p=0.26)*	1, 29 vs 38	McIntyre, 2006
ICU Length of stay (days) (all patients)	Restrictive vs liberal	Not statistically significant: 7.7±26.6 vs 6.5±40.6 λ Adjusted MD: 1.20 (95%CI: -2.13;4.53] (p=0.48)* (Figure 9)	1, 586 vs 979	Ngwenya, 2017
ICU Length of stay (days) (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 10.6±10.6 vs 9.9±14.2 Adjusted MD: 0.70 (95%CI: -2.07;3.47] (p=0.62)* (Figure 10)	1, 112 vs 203	Ngwenya, 2017
Multiple organ dysfunction	Restrictive vs liberal	Not statistically significant: 9.3±3.7 vs 8.6±3.6 MD: 0.70 [95%CI: -1.07;2.47] ¥ (p=0.44)* (Figure 11)	1, 29 vs 38 §	McIntyre, 2006
Proportion who developed infection	Restrictive vs liberal	Not statistically significant: 2/29 vs 2/38 § RR: 1.31 [95%CI: 0.20;8.76] ¥ (p=0.78)* (Figure 12)	1, 29 vs 38	McIntyre, 2006
Days requiring mechanical ventilation (all patients)	Restrictive vs liberal	Not statistically significant: 4.1±24.2 vs 4.9±21.9 λ Adjusted MD: -0.80 (95%CI: -3.19;1.59] (p=0.51)* (Figure 13)	1, 586 vs 979	Ngwenya, 2017

Days requiring mechanical ventilation (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 6.8±8.4 vs 7.8±11.3 Adjusted MD: -1.00 (95%CI: -3.20;1.20] (p=0.37)* (Figure 14)	1, 112 vs 203	Ngwenya, 2017
Days with fever (all patients)	Restrictive vs liberal	Statistically significant: Raw data not available † (p=0.01) *In favour of restrictive transfusion trigger*	1, 586 vs 979	Ngwenya, 2017
Days with fever (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 0.3±2.1 vs 0.5±2.8 Adjusted MD: -0.20 (95%CI: -0.75;0.35] ¥ (p=0.47)* (Figure 15)	1, 112 vs 203	Ngwenya, 2017
ARDS/ALI (all patients)	Restrictive vs liberal	Not statistically significant: 7/561 vs 22/848 RR: 0.48 [95%CI: 0.21;1.12] ¥ (p=0.09)* (Figure 16)	1, 561 vs 848	Ngwenya, 2017
ARDS/ALI (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 5/110 vs 15/177 § RR: 0.54 [95%CI: 0.20;1.43] ¥ (p=0.21)* (Figure 17)	1, 110 vs 177	Ngwenya, 2017
DVT/PE (all patients)	Restrictive vs liberal	Not statistically significant: 38/561 vs 46/848 RR: 1.25 [95%CI: 0.82;1.89] ¥ (p=0.30)* (Figure 18)	1, 561 vs 848	Ngwenya, 2017
DVT/PE (Patients with GCS score ≤8)	Restrictive vs liberal	Not statistically significant: 13/110 vs 18/177 § RR: 1.16 [95%CI: 0.59;2.28] ¥ (p=0.66)* (Figure 19)	1, 110 vs 177	Ngwenya, 2017

Mean ± SD (unless otherwise indicated), MD: mean difference, RR: risk ratio, OR: odds ratio, SD: standard deviation

* Calculations done by the reviewer(s) using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

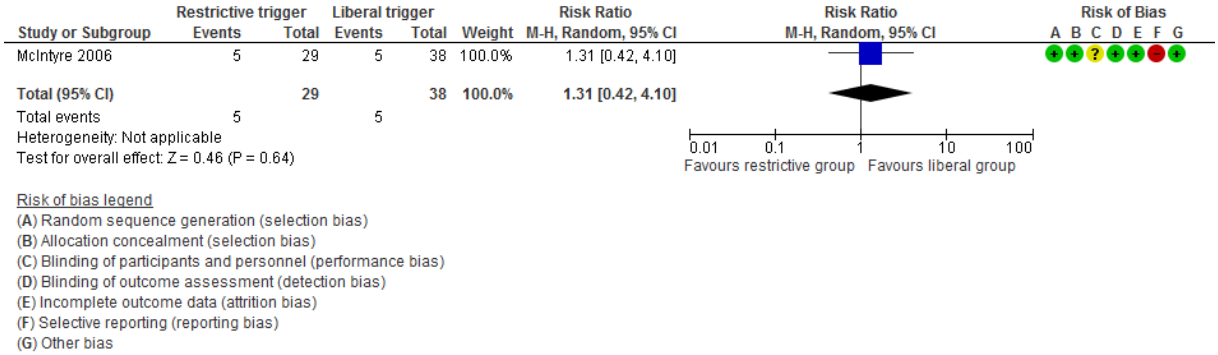


Figure 91: Forest plot of primary outcome: 30-day mortality (experimental study).

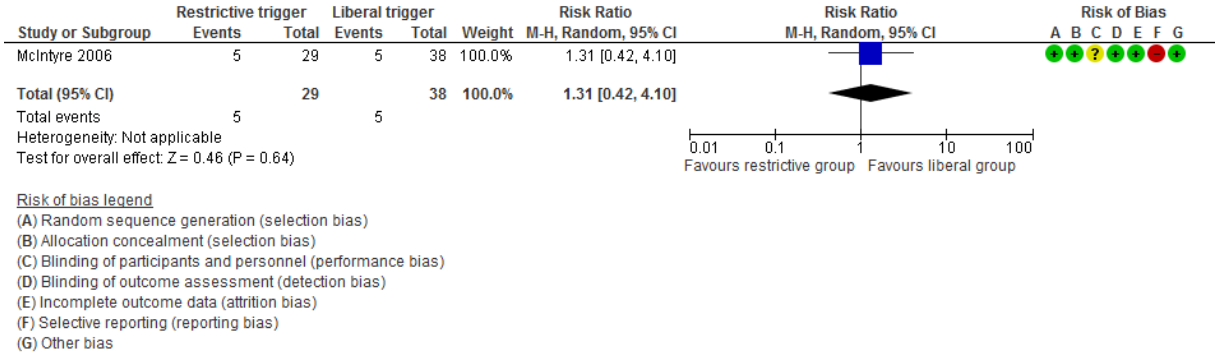


Figure 2: Forest plot of primary outcome: 60-day mortality (experimental study).

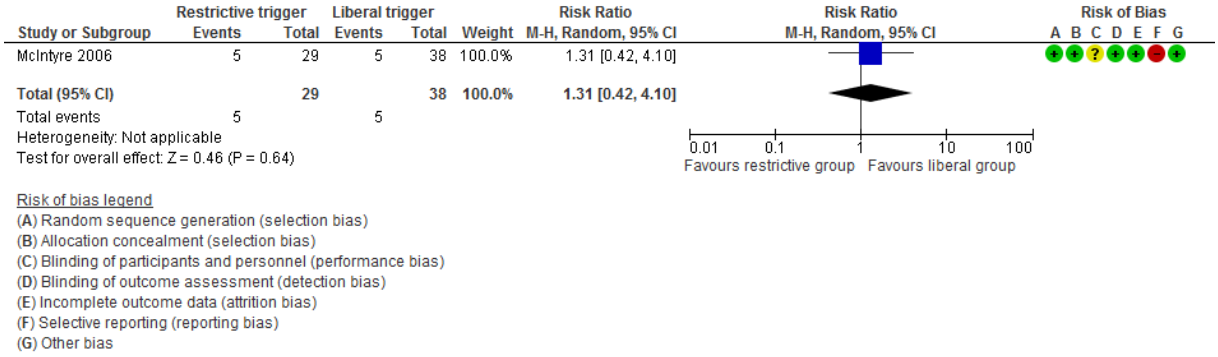


Figure 3: Forest plot of primary outcome: Hospital mortality (experimental study).

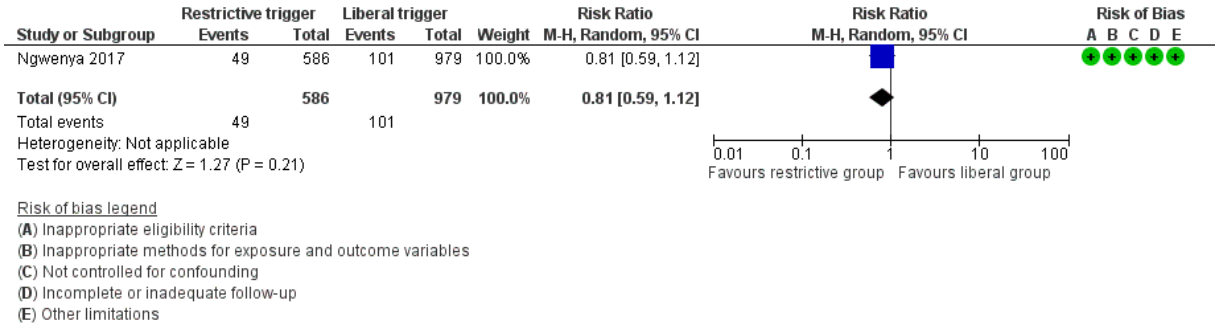


Figure 4: Forest plot of primary outcome: Hospital mortality (all patients) (observational study).

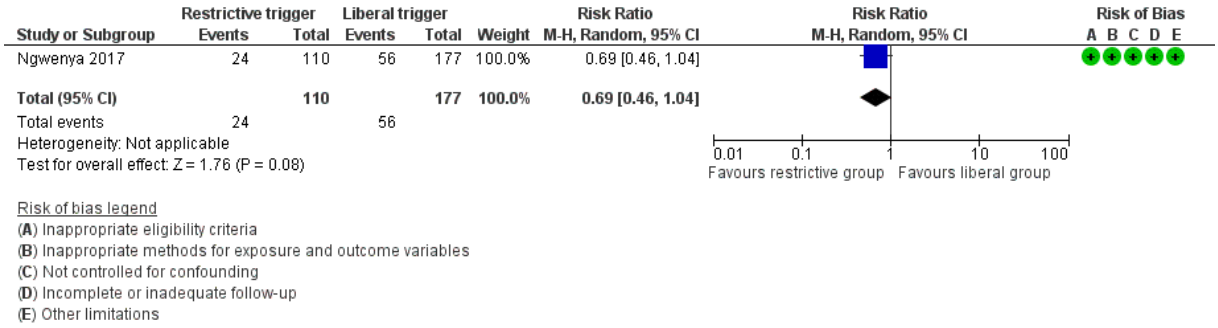


Figure 5: Forest plot of primary outcome: Hospital mortality (Patients with GCS score ≤8) (observational study).

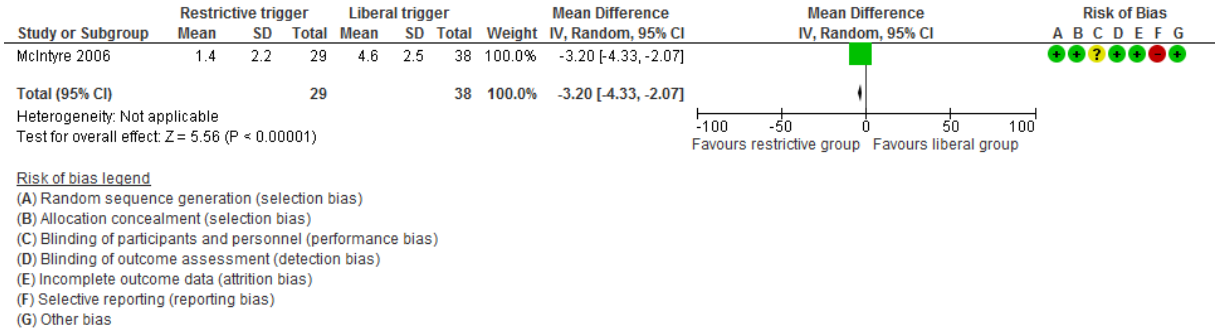


Figure 6: Forest plot of primary outcome: Number of RBC transfusions (units per patient) (experimental study study).

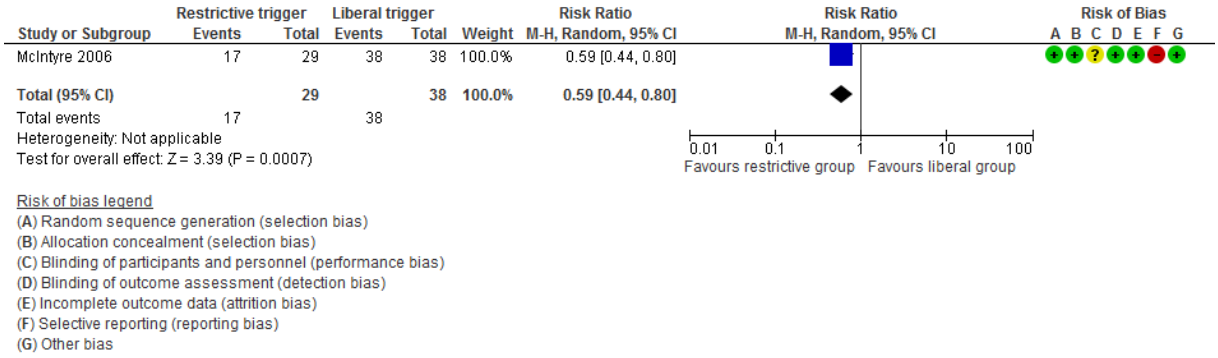


Figure 7: Forest plot of primary outcome: Proportion transfused (experimental study).

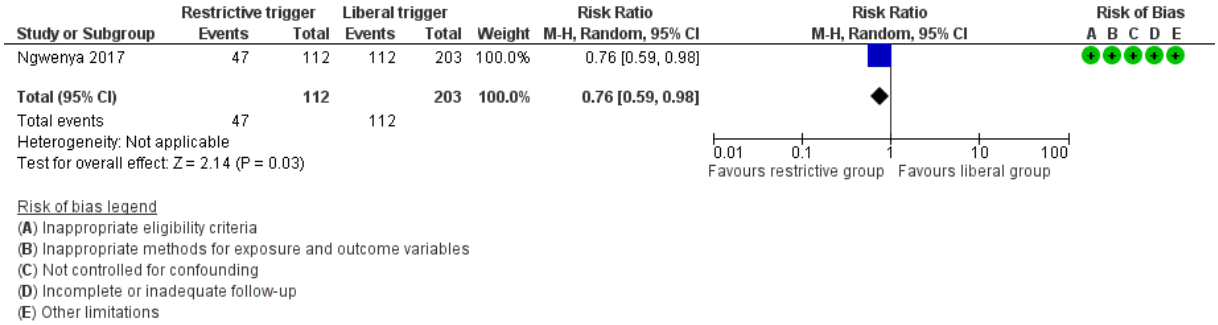


Figure 8: Forest plot of primary outcome: Patients with GCS score ≤8 that received RBC transfusion (observational study)

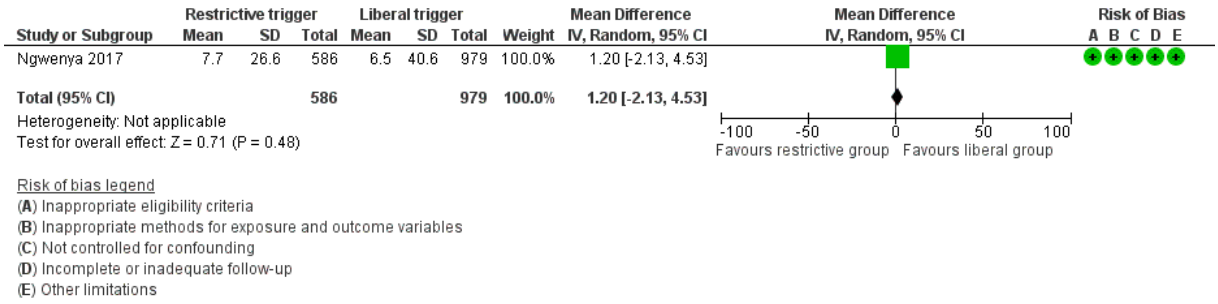


Figure 9: Forest plot of secondary outcome: ICU Length of stay (days) (all patients).

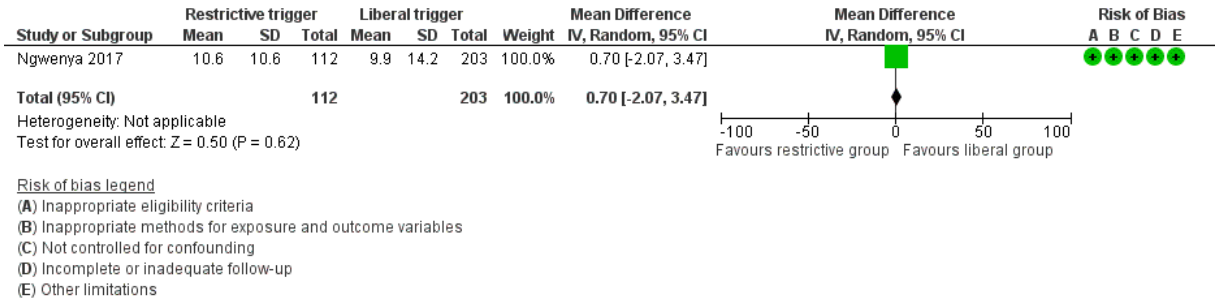


Figure 10: Forest plot of secondary outcome: ICU Length of stay (days) (Patients with GCS score ≤8) (observational study design).

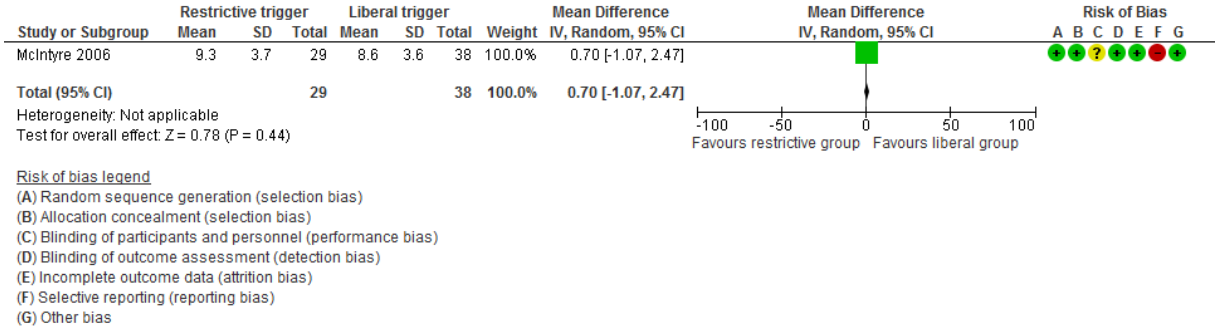


Figure 11: Forest plot of secondary outcome: Multiple organ dysfunction (experimental study design).

Figure 12: Forest plot of secondary outcome: Proportion who developed infection (experimental study design).

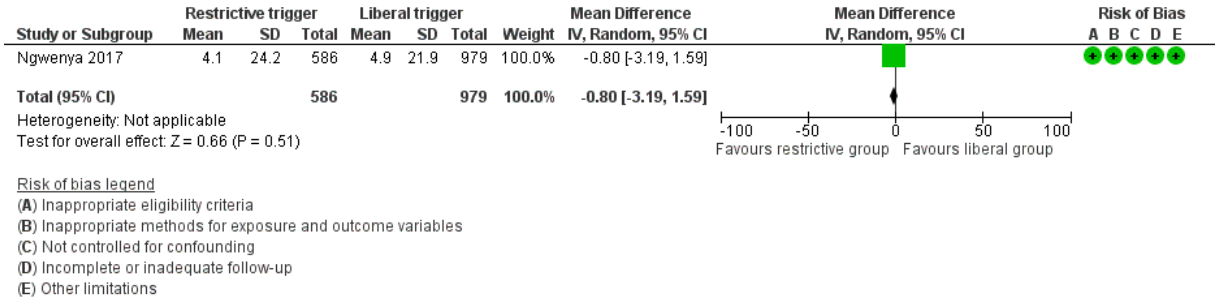


Figure 13: Forest plot of secondary outcome: Days requiring mechanical ventilation (all patients) (observation study design)

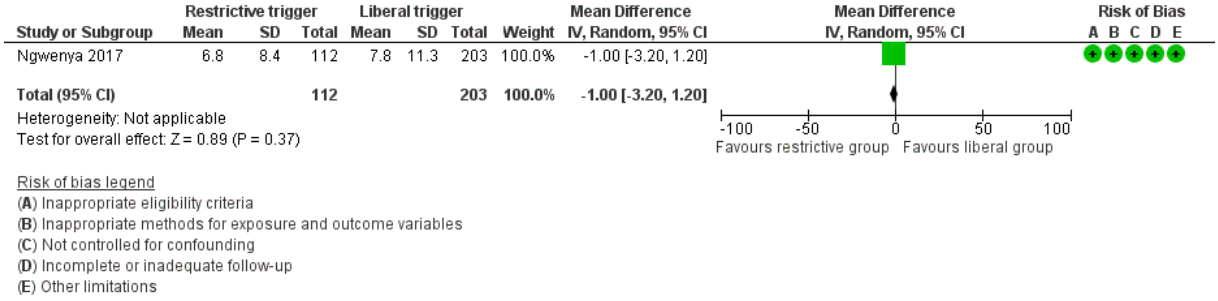


Figure 14: Forest plot of secondary outcome: Days requiring mechanical ventilation (Patients with GCS score ≤8) (observational study design)

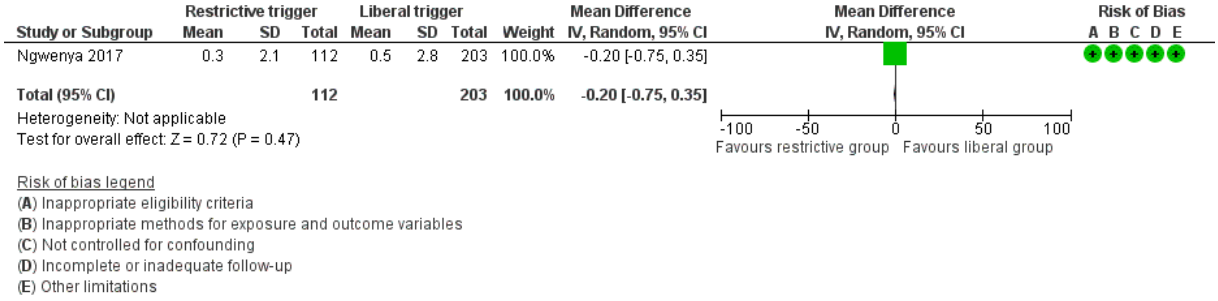


Figure 15: Forest plot of secondary outcome: Days with fever (Patients with GCS score ≤8) (observational study design).

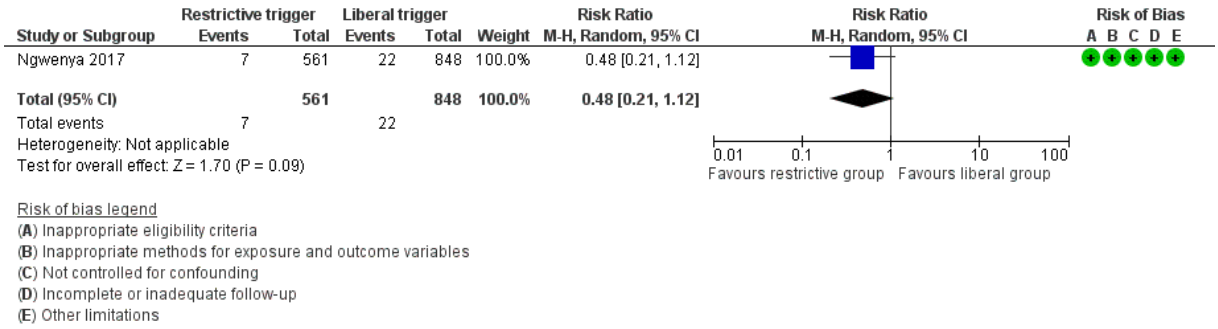


Figure 16: Forest plot of secondary outcome: Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI) (all patients) (observational study design).

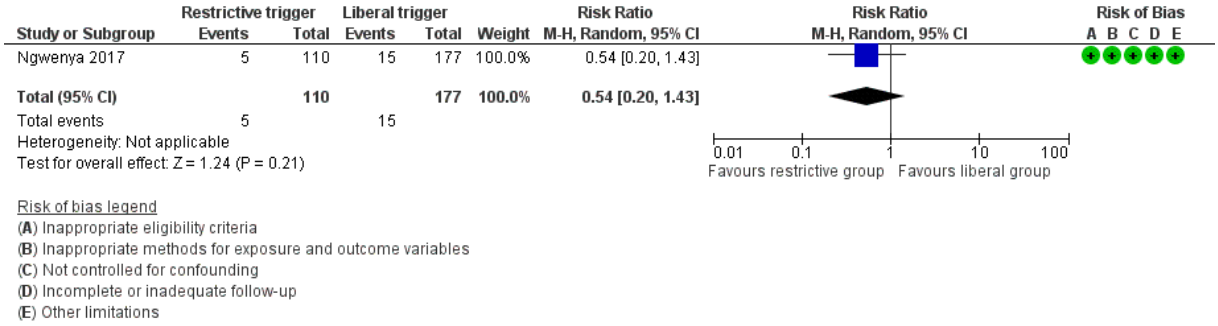


Figure 17: Forest plot of secondary outcome: Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI) (Patients with GCS score ≤8) (observational study design)

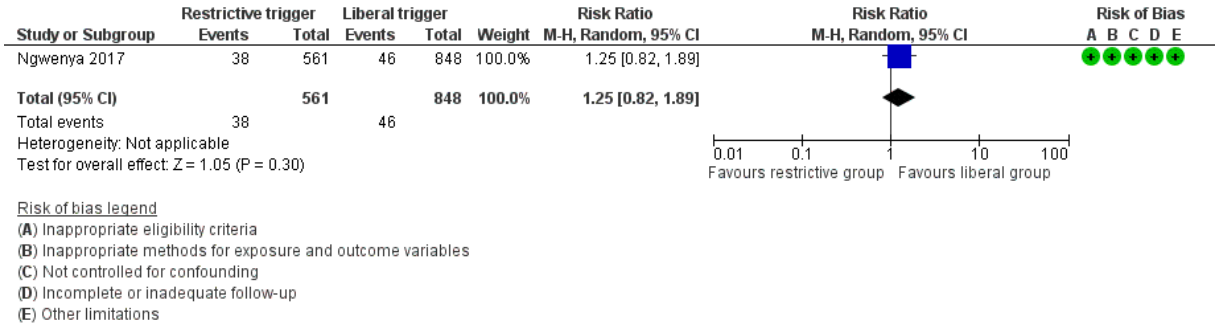


Figure 18: Forest plot of secondary outcome: Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) (all patients) (observational study design)

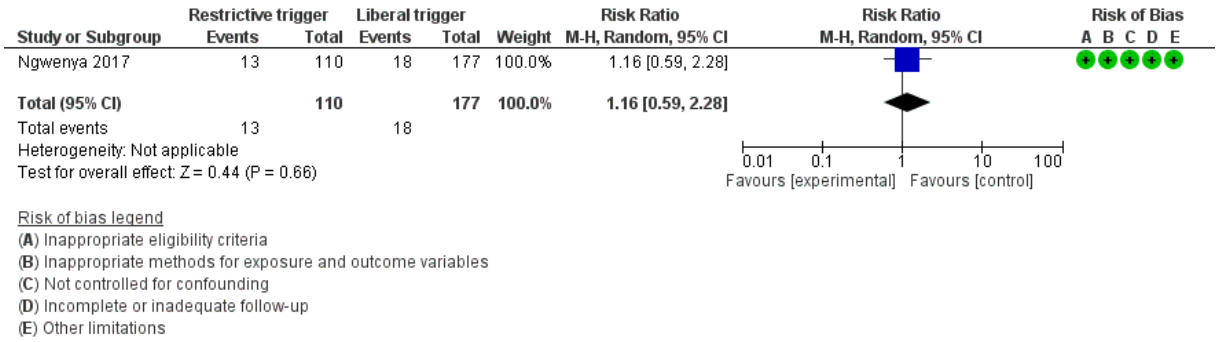


Figure 19: Forest plot of secondary outcome: Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) (Patients with GCS score ≤8) (observational study design)

Quality of evidence

Experimental studies

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
McIntyre, 2006	Randomization: No, computer generated randomization. Allocation concealment: No, sealed opaque envelopes prepared by data co-ordinating centre, opened sequentially in ICU to determine participants assignment	Participants and personnel: Unclear, unfeasible to blind personnel. Patients were in ICU. Outcome assessors: No, mortality was primary outcome and most outcomes were laboratory measures.	No	No	No

Observational studies

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
Ngwenya, 2017	No (table 2: matching for age and gender borderline)	No Because of our standardized hospital guidelines for the management of patients with TBI, all patients received identical care throughout their hospital stay, including avoidance of hypoxia and hyperglycemia, which have been shown to be risk	No Controlled for age, Injury Severity Score (ISS), Massive Transfusion Protocol (MTP) activation, number of operating room visits, and total hospital days.	No If an admission or outcomes variable was missing due to incomplete data in the Trauma Registry or medical record, pairwise deletion was used for group means and listwise deletion was used for	Retrospective study

		factors for poor outcome		regression analysis.	

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	
Reference(s)	**Articles** McIntyre LA, Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, Hare GMT, Hébert PC. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. Neurocritical Care 2006, 5:4-9. Ngwenya LB, Suen CG, Tarapore PE, Manley GT, Huang MC. *Safety and cost efficiency of a restrictive transfusion protocol in patients with traumatic brain injury*. J Neurosurg. 2017 Jun 23:1-8. **Systematic reviews** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease*. In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel

PICO 13: RBC transfusion triggers in adult patients with cerebral perfusion disorder

Overview evidence table GRADE software (PICO 13)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb<10 g/dL)**	**more liberal RBC transfusion triggers (Hb <11.5 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any packed RBC transfusion given												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	19/23 (82.6%)	20/21 (95.2%)	**RR 0.87** (0.70 to 1.07)	**124 fewer per 1.000** (from 67 more to 286 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Number of seperate packed RBC transfusions per patient												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	23	21	-	median **0 transfusion** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Packed RBC units per transfusion												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	23	21	-	median **0 units** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Total packed RBC units given per patient												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	23	21	-	median **1 units per patient fewer** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Any adverse event related to transfusion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (Hb<10 g/dL)**	**more liberal RBC transfusion triggers (Hb <11.5 g/dL)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	8/23 (34.8%)	6/21 (28.6%)	**RR 1.22** (0.51 to 2.93)	**63 more per 1.000** (from 140 fewer to 551 more)	⊕◯◯◯ VERY LOW	CRITICAL
Pulmonary edema or respiratory distress												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	8/23 (34.8%)	3/21 (14.3%)	**RR 2.43** (0.74 to 7.99)	**204 more per 1.000** (from 37 fewer to 999 more)	⊕◯◯◯ VERY LOW	CRITICAL
Any cerebral infarction on MRI												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	9/22 (40.9%)	6/20 (30.0%)	**RR 1.36** (0.59 to 3.15)	**108 more per 1.000** (from 123 fewer to 645 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Delayed cerebral infarction												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	11/23 (47.8%)	9/21 (42.9%)	**RR 1.12** (0.58 to 2.14)	**51 more per 1.000** (from 180 fewer to 489 more)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Lack of generalizibility: evidence from 1 USA study; b. Limited sample size and/or large variability in results

Detailed evidence summary (PICO 13)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with cerebral perfusion disorders (Population), is the use of a restrictive transfusion threshold (Intervention) not inferior to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: **Systematic reviews** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews) **Individual experimental studies** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 [mh stroke] OR [mh "cerebral hemorrhage"] #3 (cerebral:ti,ab OR intracerebral:ti,ab) AND hemorrhage*:ti,ab #4 CVA:ti,ab OR stroke:ti,ab OR "cerebrovascular accident":ti,ab OR "cerebrovascular accidents":ti,ab #5 #2 OR #3 OR #4 #6 #1 AND #5 (results #hits on 14 July 2017: 316 trials) **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy: **Systematic reviews**

	#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 #6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) #7 #5 AND #6 (Results #hits (on 6 July 2017): 224) **<u>Individual experimental/observational studies</u>** #1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 stroke[Mesh] OR "cerebral hemorrhage"[Mesh] #3 (cerebral[TIAB] OR intracerebral[TIAB]) AND hemorrhage*[TIAB] #4 CVA[TIAB] OR stroke[TIAB] OR "cerebrovascular accident"[TIAB] OR "cerebrovascular accidents"[TIAB] #5 #2 OR #3 OR #4 #6 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]) #7 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #8 #6 OR #7 #9 #1 AND #5 AND #8 (Results #hits (on 13 July 2017): 488) **Embase** (via Embase.com interface) using the following search strategy: **<u>Systematic reviews</u>**

	#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 #6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti #7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227) **<u>Individual experimental/observational studies</u>** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 'cerebrovascular accident'/exp OR 'brain hemorrhage'/exp #3 (cerebral:ab,ti OR intracerebral:ab,ti) AND hemorrhage*:ab,ti #4 CVA:ab,ti OR stroke:ab,ti OR 'cerebrovascular accident':ab,ti OR 'cerebrovascular accidents':ab,ti #5 #2 OR #3 OR #4 #6 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti) #7 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp) #8 #6 OR #7 #9 #1 AND #5 AND #8 (Results #hits (on 14 July 2017):1988) **Transfusion evidence library** **<u>Systematic reviews</u>** #1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit

	OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs) **Individual experimental studies** #1 Clinical specialty: Medicine – Neurological disorders #2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht #3 #1 AND #2 (results #hits on 13 July 2017: 11 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: a.) acute ischemic stroke; b.) acute intracerebral bleeding: ba: old patients (> 50yrs); bb: young pts. (< 50 yrs) **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** Included: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a

	well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Naidech, 2010, USA	Experimental: RCT	44 patients with subarachnoid hemorrhage and high risk for vasospasm • Restrictive group (n=23): mean age (±SD) = 59.2±11.9 years • Liberal group (n=21): mean age (±SD) = 54.1±14.9 years	Restrictive RBC transfusion trigger: Hb <10 g/dL Liberal RBC transfusion trigger: Hb <11.5 g/dL	This study was funded by grants to AMN from the Neurocritical Care Society, supported by Novo-Nordisk (for partial salary support) and from the Northwestern Memorial Foundation for MRI scans and additional PRBC transfusions above usual care. Periodic updates were sent to the Neurocritical Care Society, but study sponsors had no role in the design of the protocol, selection of patients, collection of data, statistical analysis, or decision to submit for publication. AMN is listed as a Co-Investigator for the proposed study Transfusion in Subarachnoid Hemorrhage (PI: Peter D LeRoux), and some of these data have been used to plan it. The grant has not yet been submitted, and there has been no compensation (financial or

				otherwise) for that study.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
PRIMARY OUTCOMES				
Any packed RBC transfusion given	Restrictive vs liberal	Not statistically significant: 19/23 vs 20/21 RR 0.87 [95%CI: 0.70; 1.07] ¥ (p=0.19)* (Figure 1)	1, 23 vs 21 §	Naidech, 2010
Number of separate packed RBC transfusions per patient	Restrictive vs liberal	Not statistically significant: 2 (1-3) (median, Q1-Q3) vs 2 (1-4), median difference 0 (IQR could not be calculated) (p>0.05)	1, 23 vs 21 §	Naidech, 2010
Packed RBC units per transfusion	Restrictive vs liberal	Statistically significant: 1 (1-1) (median, Q1-Q3) vs 1 (1-2) (p<0.05) *In favour of restrictive transfusion trigger*	1, 23 vs 21 §	Naidech, 2010
Total packed RBC units given per patient	Restrictive vs liberal	Not statistically significant: 2 (1-3) (median, Q1-Q3) vs 3 (2-4), median difference -1 (IQR could not be calculated) (p=0.05)	1, 23 vs 21 §	Naidech, 2010
SECONDARY OUTCOMES				
Days to first transfusion	Restrictive vs liberal	Not statistically significant: 3.8±5.2 vs 2.3±1.9 MD 1.50 (95%CI: -0.78; 3.78] ¥ (p=0.20)* (Figure 2)	1, 23 vs 21 §	Naidech, 2010
Days to last transfusion	Restrictive vs liberal	Not statistically significant: 8.5±4.8 vs 6.7±5.1 MD 1.80 (95%CI: -1.13;4.73] ¥ (p=0.23)* (Figure 3)	1, 23 vs 21 §	Naidech, 2010
Any adverse event related to transfusion	Restrictive vs liberal	Not statistically significant: 8/23 vs 6/21 RR 1.22 [95%CI: 0.51;2.93] ¥ (p=0.66)* (Figure 4)	1, 23 vs 21 §	Naidech, 2010
Days with fever ≥ 100.4F core	Restrictive vs liberal	Not statistically significant: 7 (2-11) (median, Q1-Q3) vs 5 (1-8.5), median difference 2 (IQR could not be calculated) (p>0.05)	1, 23 vs 21 §	Naidech, 2010
Pulmonary edema or respiratory distress	Restrictive vs liberal	Not statistically significant: 8/23 vs 3/21 RR 2.43 [95%CI: 0.74;7.99] ¥ (p=0.14)* (Figure 5)	1, 23 vs 21 §	Naidech, 2010
Rash	Restrictive vs liberal	Not statistically significant: 0/23 vs 1/21	1, 23 vs 21 §	Naidech, 2010

		RR 0.31 [95%CI: 0.01;7.12] ¥ (p=0.46)* (Figure 6)		
Hypotension	Restrictive vs liberal	Not statistically significant: 1/23 vs 1/21 RR 0.91 [95%CI: 0.06;13.69] ¥ (p=0.95)* (Figure 7)	1, 23 vs 21 §	Naidech, 2010
Ventilator-free day (max 14)	Restrictive vs liberal	Not statistically significant: 14 (5-14) (median, Q1-Q3) vs 12 (6.5-14), median difference 2 (IQR could not be calculated) (p>0.05)	1, 23 vs 21 §	Naidech, 2010
Symptomatic vasospasm	Restrictive vs liberal	Not statistically significant: 5/23 vs 5/21 RR 0.91 [95%CI: 0.31;2.71] ¥ (p=0.87)* (Figure 8)	1, 23 vs 21 §	Naidech, 2010
Any cerebral infarction on MRI	Restrictive vs liberal	Not statistically significant: 9/22 vs 6/20 RR 1.36 [95%CI: 0.59;3.15] ¥ (p=0.47)* (Figure 9)	1, 22 vs 20 §	Naidech, 2010
Delayed cerebral infarction	Restrictive vs liberal	Not statistically significant: 11/23 vs 9/21 RR 1.12 [95%CI:0.58;2.14] ¥ (p=0.74)* (Figure 10)	1, 23 vs 21 §	Naidech, 2010

Mean ± SD (unless otherwise indicated), MD: mean difference, RR: risk ratio, OR: odds ratio, SD: standard deviation

* Calculations (specifieer welke waarden precies) done by the reviewer(s) using Review Manager software (plaats symbool: na hetgene je berekend hebt; in geval van meerdere zaken zelf berekend: ster helemaal onderaan (na p-waarde))

* Calculations (weighted mean and pooled SD, based on the means and SDs of the individual studies) done by the reviewer using Excel (dit is het geval voor Cochrane SRs waar enkel de pooled MD en CI gegeven zijn)

£ No raw data/SD's available (or specify), effect size and CI cannot be calculated (Use ££ or £££ if necessary) (plaats symbool: waar data ontbreken)

¥ Imprecision (large variability of results) (plaats symbool: na CI)

† Imprecision (lack of data) (na £)

§ Imprecision (limited sample size or low number of events) (plaats symbool: na # participants in geval van limited sample size; na breuken in geval van low number of events of na #participants als number of events niet gegeven is maar sample size <300)

λ data extracted from graph

Forest plots

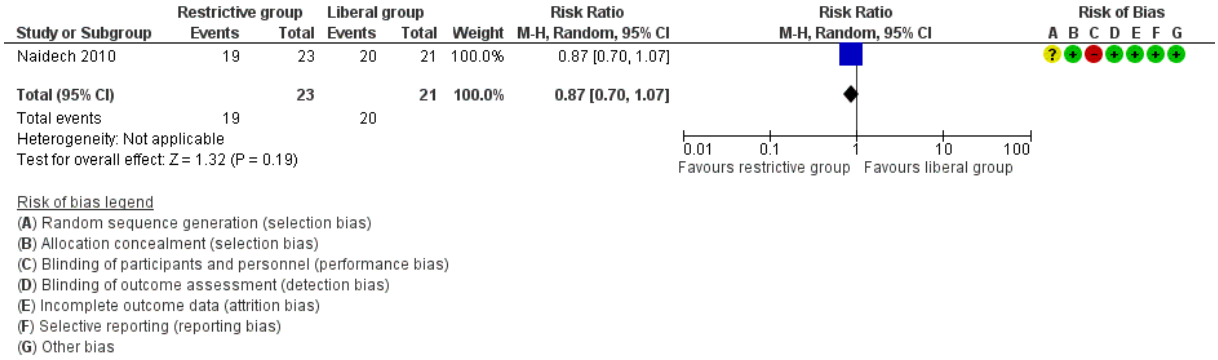


Figure 92: Forest plot of outcome: Any packed RBC transfusion given.

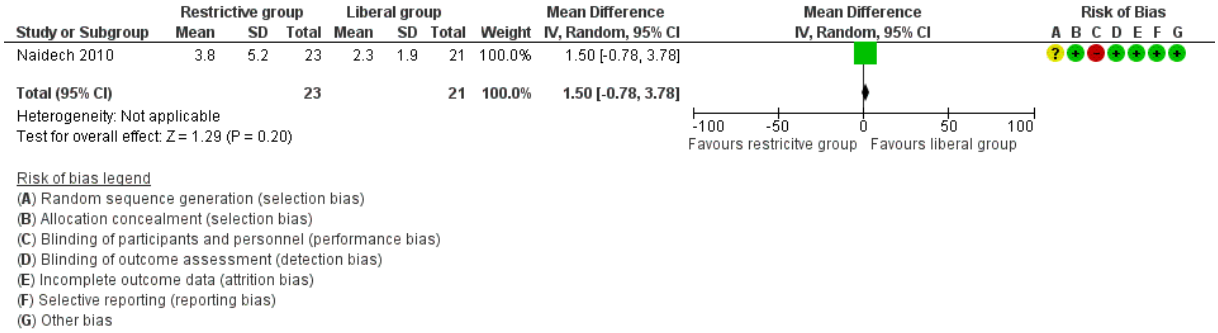


Figure 2: Forest plot of outcome: Days to first transfusion.

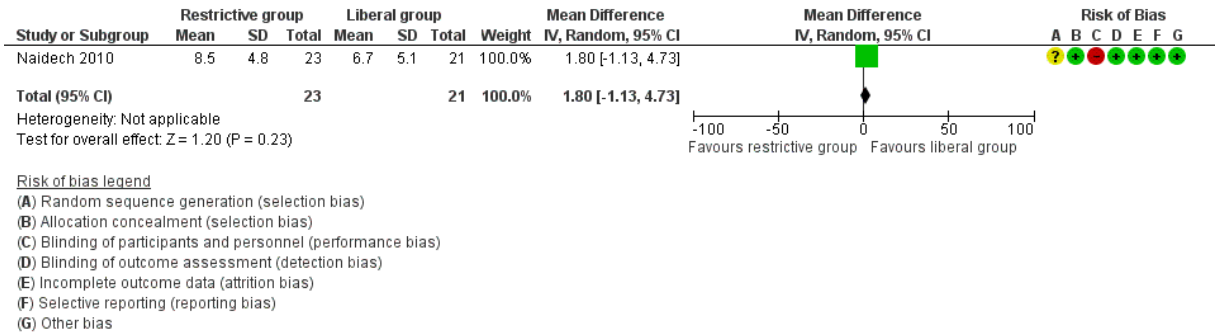


Figure 3: Forest plot of outcome: Days to last transfusion.

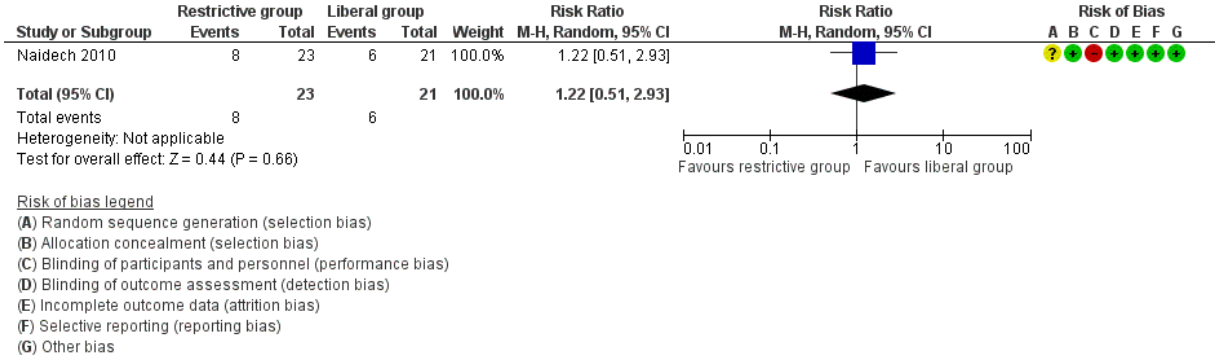


Figure 4: Forest plot of outcome: Any adverse event related to transfusion.

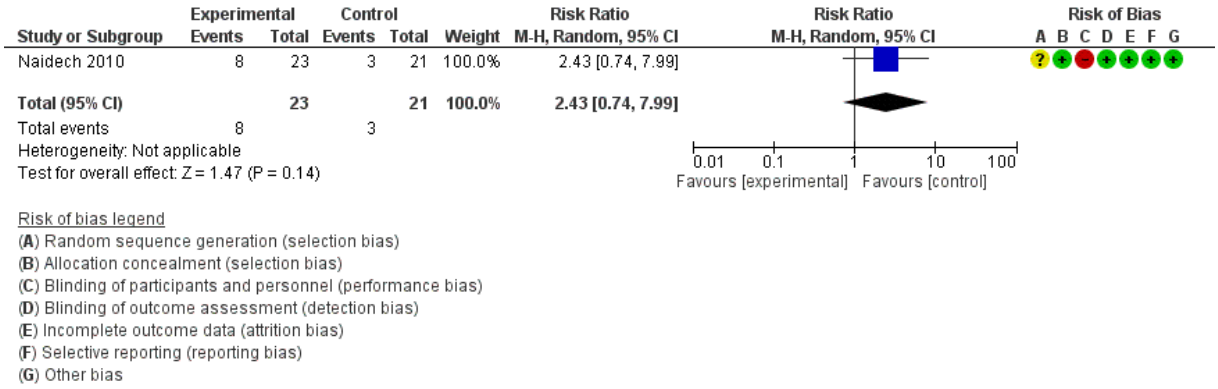


Figure 5: Forest plot of outcome: Pulmonary edema or respiratory distress.

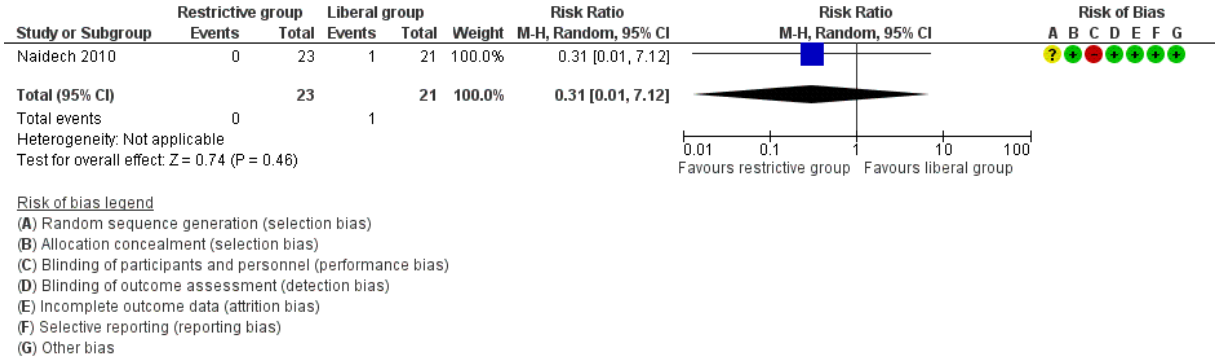


Figure 6: Forest plot of outcome: Rash.

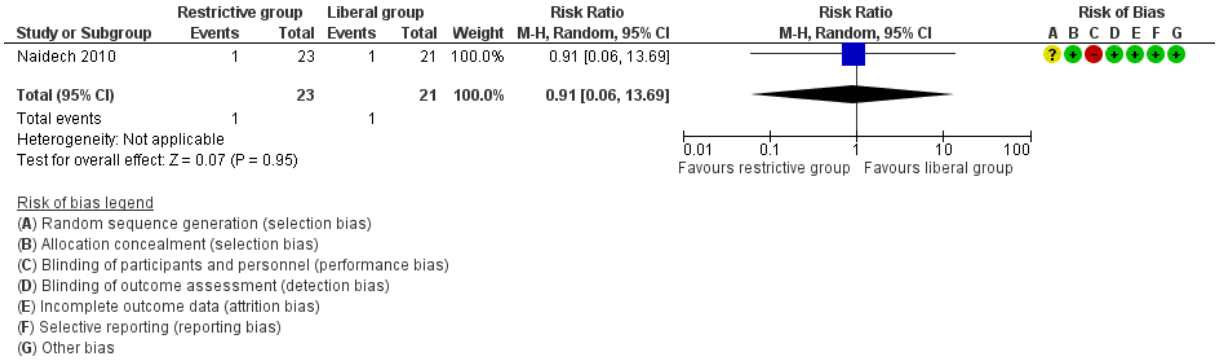


Figure 7: Forest plot of outcome: Hypotension.

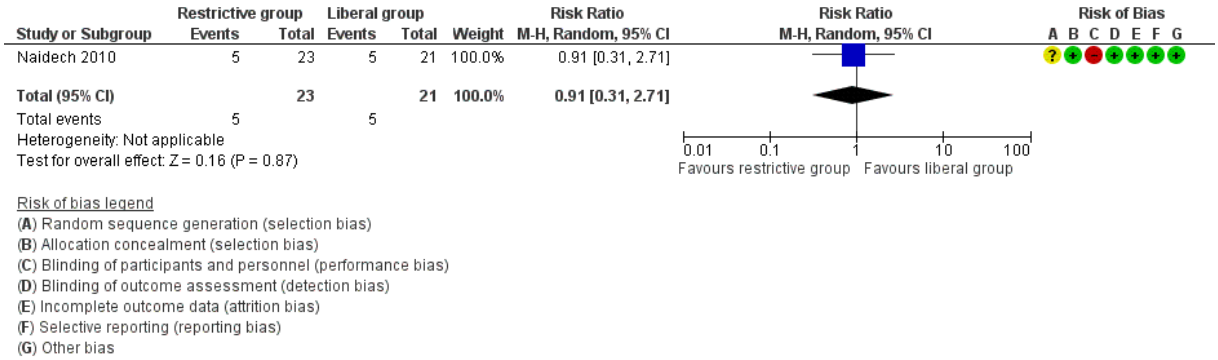


Figure 8: Forest plot of outcome: Symptomatic vasospasm.

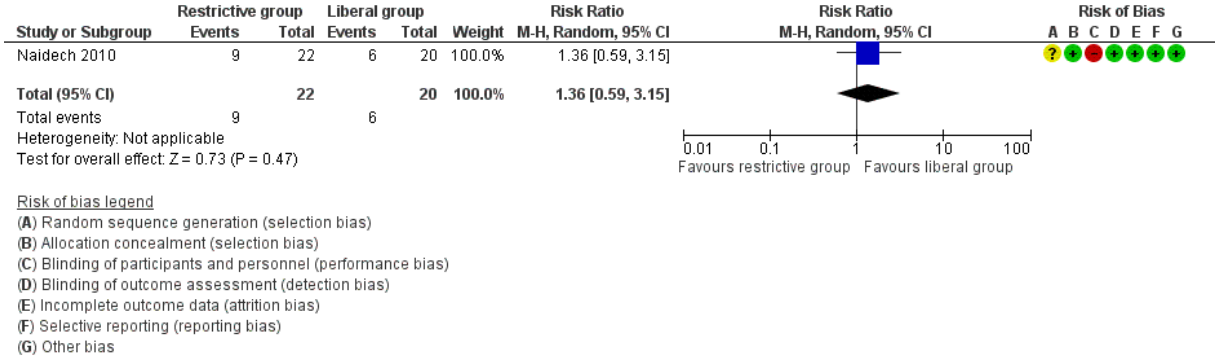


Figure 9: Forest plot of outcome: Any cerebral infarction on MRI.

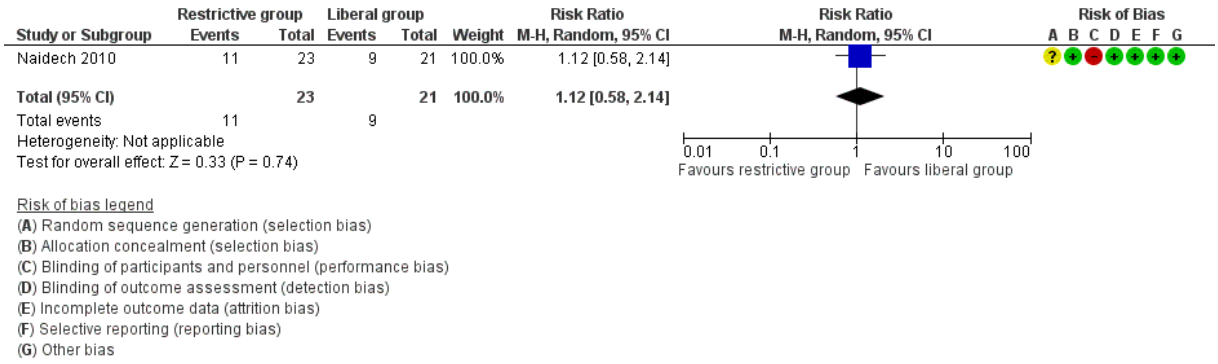


Figure 10: Forest plot of outcome: Delayed cerebral infarction.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Naidech, 2010	Randomization: unclear Allocation concealment: no (sealed opaque sequentially numbered envelopes were used)	Participants and personnel: yes (participants and personnel were not blinded) Outcome assessors: no (All the MRI scans were performed by a single certified neuro-radiologist who was blinded to clinical treatment. A blinded vascular neurologist ascertained the NIH Stroke Scale)	No	No	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**<u>Articles</u>** **Naidech 2010** Naidech AM, Shaibani A, Garg RK, Duran IM, Liebling SM, Bassin SL, Bendok BR, Bernstein RA, Batjer HH, Alberts MJ. *Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage*. Neurocrit Care. 2010; 13(3):313-320. **<u>Systematic reviews</u>** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease.* In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel

PICO 14: RBC transfusion triggers in adult patients with acute bleeding

Overview evidence table GRADE software (PICO 14)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more restrictive RBC transfusion triggers (70-80% of RBC volume)**	**more liberal RBC transfusion triggers (100% of RBC volume)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Blood usage (units)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	12	10	-	MD **6.5 units lower** (12.21 lower to 0.79 lower)	⨁⨁◯◯ LOW	IMPORTANT
Number of participants transfused												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	8/12 (66.7%)	10/10 (100.0%)	**RR 0.68** (0.45 to 1.04)	**320 fewer per 1.000** (from 40 more to 550 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Selection, detection and performance bias unclear

b. Study of 1956 (not generalizible to 2018)

c. Limited sample size and large variability in results

Detailed evidence summary (PICO 14)

Topic	Patient Blood Management
Subtopic	Evidence-based transfusion strategies: RBC transfusion triggers
Intervention	Restrictive RBC transfusion triggers
Question (PICO)	In patients with acute bleeding (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusion threshold (Comparison)?
Search Strategy	The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to: - Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017) - Identify observational studies in case no experimental studies were available. Databases **The Cochrane Library** (systematic reviews and controlled trials) using the following search strategy: **Systematic reviews** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 Results #hits (on Wednesday 6 July: 25 Cochrane reviews) **Individual experimental studies** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 (acute:ti,ab OR massive:ti,ab) AND (bleeding:ti,ab OR hemorrhage*:ti,ab OR "blood loss":ti,ab) #3 #1 AND #2 (results #hits on 14 July 2017: 170 trials) **MEDLINE** (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy: **Systematic reviews** #1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR

	strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI])) #2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI])) #3 (blood[TI] AND (management[TI] OR program*[TI])) #4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI])) #5 #1 OR #2 OR #3 OR #4 #6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))) #7 #5 AND #6 (Results #hits (on 6 July 2017): 224) **<u>Individual experimental/observational studies</u>** #1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI])) #2 (acute[TIAB] OR massive [TIAB]) AND (bleeding[TIAB] OR hemorrhage*[TIAB] OR "blood loss"[TIAB]) #3 ("Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-control"[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR "cohort study"[TIAB] OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR "longitudinal"[TIAB] OR "retrospective"[TIAB] OR "cross sectional"[TIAB] OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]) #4 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "metaanalysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) #5 #3 OR #4 #6 #1 AND #2 AND #5 (Results #hits (on 13 July 2017): 450) **Embase** (via Embase.com interface) using the following search strategy: **<u>Systematic reviews</u>** #1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti)) #2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR

	threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti)) #3 (blood:ti AND (management:ti OR program*:ti)) #4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti)) #5 #1 OR #2 OR #3 OR #4 #6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti #7 #5 AND #6 (systematic reviews) (Results #hits on 6 July 2017: 227) **<u>Individual experimental/observational studies</u>** #1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti)) #2 (acute:ab,ti OR massive:ab,ti) AND (bleeding:ab,ti OR hemorrhage*:ab,ti OR "blood loss":ab,ti) #3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti) #4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp) #5 #3 OR #4 #6 #1 AND #2 AND #5 (Results #hits (on 14 July 2017): 1480) **Transfusion evidence library** **<u>Systematic reviews</u>** #1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding) #2 systematic review filter #3 #1 AND #2 (results #hits on 6 July 2017: 427 SRs) **<u>Individual experimental studies</u>** #1 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht

	#2 (acute OR massive) AND (bleeding OR hemorrhage* OR "blood loss") #3 #1 AND #2 (results #hits on 14 July 2017: 561 RCTs)
Search date	13/11/2017 (Cochrane review 2016 + updated/unpublished review Carson 2018) 26/01/2018 (update after latest search date Carson review)
In/Exclusion criteria	**Population:** Included: patients with acute bleeding: clinically instable bleeding patients undergoing massive transfusion: a.) trauma-induced bleeding; b.) non-trauma induced bleeding **Intervention:** the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL. **Comparison:** the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL. **Outcomes:** *Primary:* Mortality (30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue). **Study design:** Included: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) individual (cluster) randomized controlled trials not included in a systematic review or 3) observational studies if no experimental studies were identified. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without hemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Study funding, financial COI and remarks
Fisher, 1956, United Kingdom	Experimental: randomised controlled trial	22 trauma participants were randomly allocated to 1 of 2 groups: • Liberal group: n = 10 • Restrictive group: n = 12 NB: no demographic data were reported.	Restrictive RBC transfusion trigger: an attempt was made to leave the RBC volume at the end of resuscitation at 70% to 80% of normal. Liberal RBC transfusion trigger: the aim was to achieve 100% or more of the RBC volume at the end of resuscitation.	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
PRIMARY OUTCOMES				
Blood usage (units)	Restrictive vs liberal	Statistically significant: 4.8±6.7 vs 11.3±6.9 MD: -6.50 [95%CI: -12.21;-0.79] (p=0.03)* (Figure 1) *In favour of restrictive transfusion trigger*	1, 12 vs 10 §	Fisher 1956
Number of participants transfused	Restrictive vs liberal	Not statistically significant: 8/12 vs 10/10 RR: 0.68 [95%CI: 0.45;1.04] ¥ (p=0.07)* (Figure 2)	1, 12 vs 10 §	Fisher 1956

Mean ± SD (unless otherwise indicated), MD: mean difference, RR: risk ratio, OR: odds ratio, SD: standard deviation

* Calculations done by the reviewer using Review Manager software

¥ Imprecision (large variability of results)

§ Imprecision (limited sample size or low number of events)

Forest plots

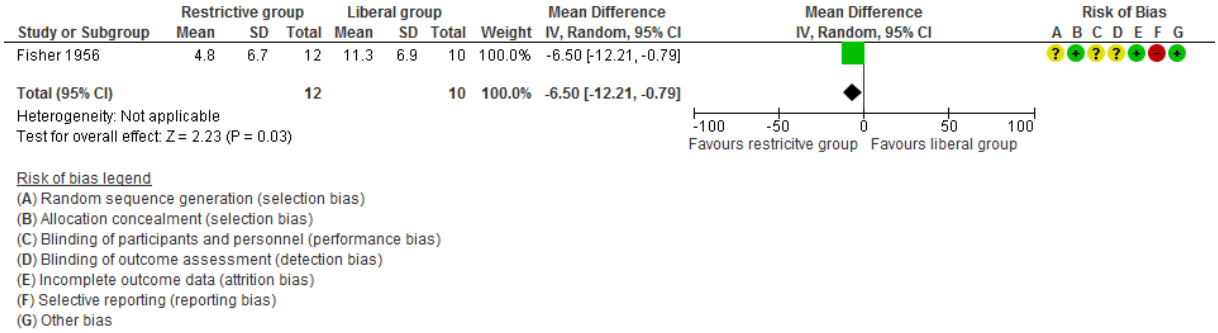


Figure 93: Forest plot of outcome: Blood usage (units).

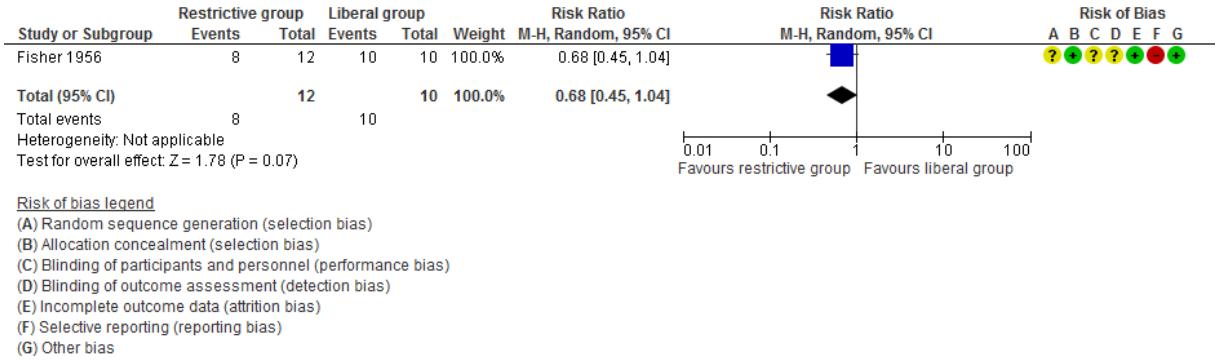


Figure 2: Forest plot of outcome: Number of participants transfused.

Quality of evidence

Author, Year	Lack of allocation concealment and random sequence generation (selection bias)	Lack of blinding (performance bias)	Incomplete accounting of outcome events (attrition bias)	Selective outcome reporting (reporting bias)	Other limitations
Fisher, 1956	Randomization: Unclear The use of random sequence generation was not described Allocation concealment: No The trial used sealed envelopes. When the participant was considered eligible for the trial, they were placed in a severity grade and an envelope was opened to decide which transfusion schedule was to be used.	Participants and personnel: Unclear Blinding of participants and personnel was not addressed Outcome assessors: Unclear Blinding of outcome assessment was not addressed	No The data set appeared to be complete	Yes No pre-registration of study protocol	No

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	**Articles** **Fisher 1956** Fisher MR and Topley ET. *The illness of trauma.* British Journal of Clinical Practice 1956, 10(11): 770-776. **Systematic reviews** Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC. *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev. 2016, 10:CD002042. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, Goodman SG, Rao SV, Doree C, Hebert PC. *Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease.* In peer-review [February 2018].
Evidence used for	Consensus meeting PBM
Project	PBM
Reviewer(s)	Hans Van Remoortel