INTERNATIONAL CONSENSUS CONFERENCE
ICC·PBM
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ICC-PBM 2018: PRESENTATIONS PICO QUESTIONS RBC TRANSFUSION TRIGGERS

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Presentation Research Evidence during parallel sessions: 3 subtopics

- ✓ Acute interventions – intensive care (7 PICO's) **(Cécile Aubron & Jerrold Levy)**
  - ✓ Critically ill intensive care patients
  - ✓ Septic shock
  - ✓ Orthopaedic and (non-)cardiac surgery
  - ✓ Cardiac surgery
  - ✓ Coronary heart disease
  - ✓ Acute gastrointestinal bleeding
  - ✓ Acute bleeding
- ✓ Haematology & Oncology (2 PICO's) **(Richard Gammon)**
- ✓ Neurology (2 PICO's) **(Cynthia So-Osman)**
  - ✓ Acute CNS injury
  - ✓ Cerebral perfusion disorders

PICO questions

Should more restrictive RBC transfusion triggers *(**Intervention**)* versus more liberal RBC transfusion triggers *(**Comparison**)* be used in

- Critically ill, but clinically stable intensive care patients (adults)? *(**Population 1**)*
- Adult patients with septic shock? *(**Population 2**)*

- Adult patients with orthopaedic and non-cardiac surgery? *(**Population 3**)*
- Adult patients with coronary heart disease? *(**Population 4**)*
- Adult patients with cardiac surgery? *(**Population 5**)*

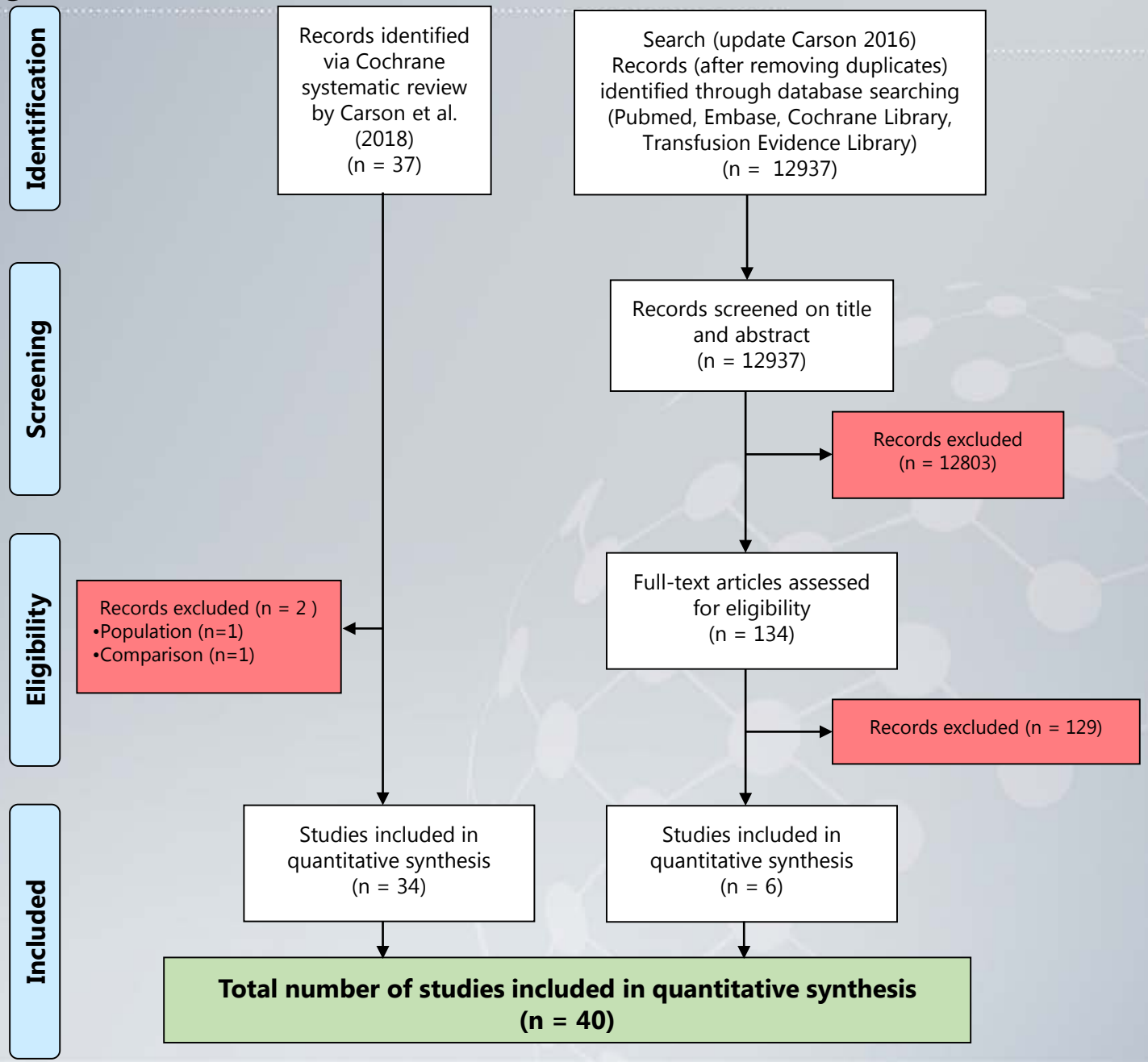
- Adult patients with acute (gastrointestinal) bleeding? *(**Population 6/7**)*

- Adult patients with haematological diseases? *(**Population 8**)*
- Adult patients with solid tumours? *(**Population 9**)*

- Adult patients with acute central nervous system injury? *(**Population 10**)*
- Adult patients with cerebral perfusion disorders? *(**Population 11**)*

Outcomes of interest: clinical outcomes: mortality, morbidity-related outcomes that occured during hospitalisation, RBC utilization

Flow chart


Identification
Screening
Eligibility
Included
Records identified via Cochrane systematic review by Carson et al. (2018) (n = 37)
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 = 2) •Population (n=1) •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)

Acute interventions & intensive care

Critically ill, stable ICU
Septic shock

Cécile Aubron

Study characteristics

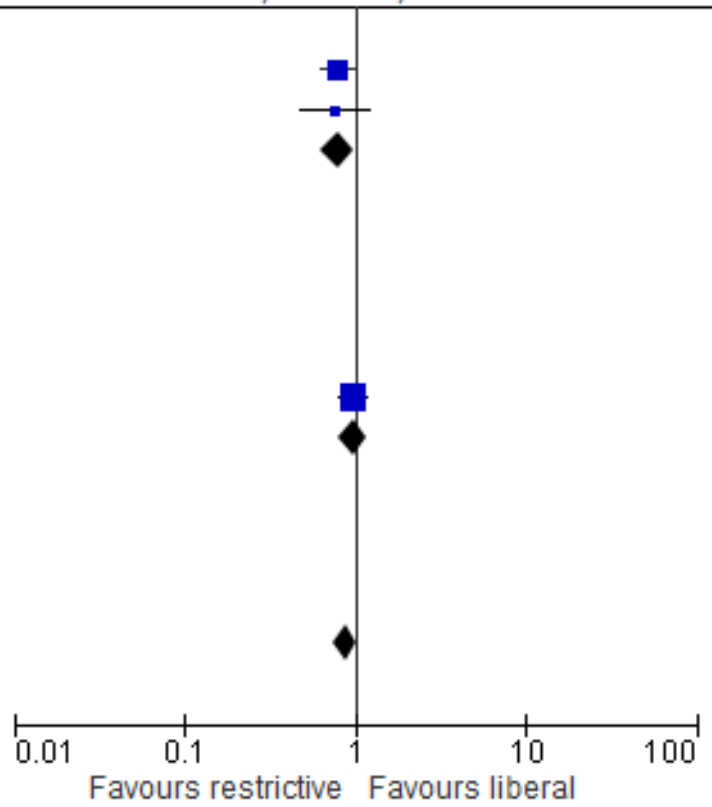
Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Bergamin, 2017, Brazil	RCT	300 adult cancer patients with septic shock in the first 6 hours of ICU admission.	RBC transfusion (1 unit) if Hb <7 g/dL	RBC transfusion (1 unit) if Hb <9 g/dL
Hébert, 1995, Canada	RCT	69 normovolaemic critically ill participants admitted to a tertiary level intensive care unit	RBC transfusion if 7.0<Hb<7.5 g/dL, maintained at 7.0-9.0 g/dL	RBC transfusion if 10.0<Hb<10.5 g/dL, maintained at 10.0-12.0 g/dL
Hébert, 1999, Canada	RCT	838 critically ill participants with euvolaemia after initial treatment admitted to ICU	RBC transfusion if Hb <7.0 g/dL, and then maintained at 7.0-9.0 g/dL	RBC transfusion if Hb <10.0 g/dL, and then maintained at 10.0-12.0 g/dL
Holst, 2014, Denmark	RCT	998 participants in Denmark, Sweden, Norway and Finland with septic shock in the ICU	RBC transfusion if Hb conc ≤7.0 g/dL	Liberal group (control): transfusion if Hb ≤9.0 g/dL
Palmieri, 2017, USA	RCT	Eighteen burn centers enrolled 345 patients with 20% or more total body surface area burn.	RBC transfusion if Hb <7.0 g/dL, target Hb 7.0-8.0 g/dL	RBC transfusion if Hb <10.0 g/dL, target Hb 10.0-11.0 g/dl
Walsh, 2013, UK	RCT	ICU participants ≥55 years, Hb <9 g/dL, mechanical ventilation for ≥ 96 hours, and expected to require ≥ 24 hours of further mechanical ventilation	RBC transfusion if Hb <7.0 g/dL, target Hb 7.1-9.0 g/dL	RBC transfusion if Hb <9.0 g/dL, target Hb 9.1-11.0 g/dL

Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: hospital mortality

Study or Subgroup	Restrictive Events	Total	Liberal Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Critically ill, stable ICU						
Hébert 1999	93	418	118	420	35.9%	0.79 [0.63, 1.00]
Walsh 2013	19	51	24	49	10.3%	0.76 [0.48, 1.20]
Subtotal (95% CI)		**469**		**469**	**46.2%**	**0.79 [0.64, 0.97]**
Total events	112		142			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
1.2.2 Septic shock						
Holst 2014	151	502	154	496	53.8%	0.97 [0.80, 1.17]
Subtotal (95% CI)		**502**		**496**	**53.8%**	**0.97 [0.80, 1.17]**
Total events	151		154			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**971**		**965**	**100.0%**	**0.88 [0.76, 1.02]**
Total events	263		296			
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 2 (P = 0.34); I² = 8%						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: Chi² = 2.15, df = 1 (P = 0.14), I² = 53.5%						

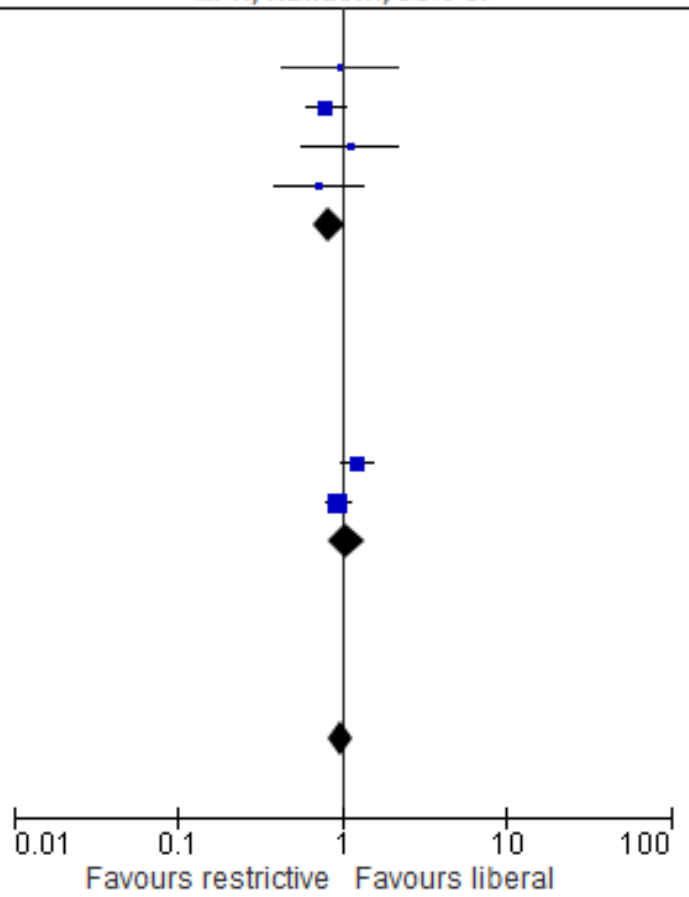


Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: 30-day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Critically ill, stable ICU						
Hébert 1995	8	33	9	36	3.8%	0.97 [0.42, 2.22]
Hébert 1999	78	418	98	420	23.0%	0.80 [0.61, 1.04]
Palmieri 2017	16	168	15	177	5.6%	1.12 [0.57, 2.20]
Walsh 2013	12	51	16	49	6.1%	0.72 [0.38, 1.36]
Subtotal (95% CI)		**670**		**682**	**38.5%**	**0.83 [0.67, 1.04]**
Total events	114		138			
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
1.1.2 Septic shock						
Bergamin 2017	84	151	67	149	27.0%	1.24 [0.99, 1.55]
Holst 2014	168	502	175	496	34.4%	0.95 [0.80, 1.13]
Subtotal (95% CI)		**653**		**645**	**61.5%**	**1.07 [0.83, 1.39]**
Total events	252		242			
Heterogeneity: Tau² = 0.03; Chi² = 3.38, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 0.52 (P = 0.60)						
Total (95% CI)		**1323**		**1327**	**100.0%**	**0.97 [0.82, 1.15]**
Total events	366		380			
Heterogeneity: Tau² = 0.01; Chi² = 7.62, df = 5 (P = 0.18); I² = 34%						
Test for overall effect: Z = 0.31 (P = 0.75)						
Test for subgroup differences: Chi² = 2.12, df = 1 (P = 0.15), I² = 52.8%						



‘Acute intervention & intensive care’

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: 30-day mortality (subgroup analyses)

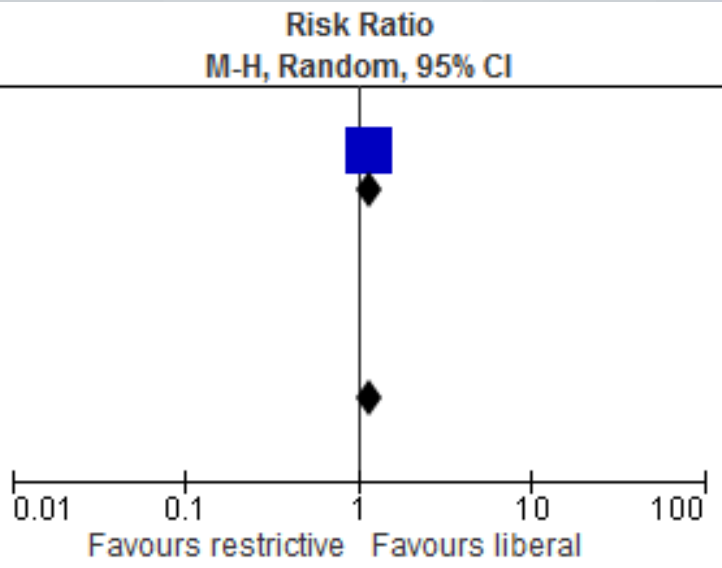
Outcomes	Difference (restrictive (< 7-8 g/dL) versus liberal (<9-10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
30-day mortality (subgroup: less severe patients (APACHE-score 20 or less))	**74 fewer per 1.000** (110 fewer to 13 fewer)	**RR 0.54** (0.32 to 0.92)
30-day mortality (subgroup: younger patients (<55 years))	**73 fewer per 1.000** (102 fewer to 12 fewer)	**RR 0.44** (0.22 to 0.91)
30-day mortality (subgroup: cardiac disease)	**23 fewer per 1.000** (94 fewer to 82 more)	**RR 0.90** (0.59 to 1.36)
30-day mortality (subgroup: severe infections and septic shock)	**69 fewer per 1.000** (152 fewer to 60 more)	**RR 0.77** (0.49 to 1.20)

Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: 60-day mortality

Study or Subgroup	Restrictive Events	Total	Liberal Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Septic shock						
Bergamin 2017	99	151	84	149	100.0%	1.16 [0.97, 1.40]
Subtotal (95% CI)		**151**		**149**	**100.0%**	**1.16 [0.97, 1.40]**
Total events	99		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
Total (95% CI)		**151**		**149**	**100.0%**	**1.16 [0.97, 1.40]**
Total events	99		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
Test for subgroup differences: Not applicable						

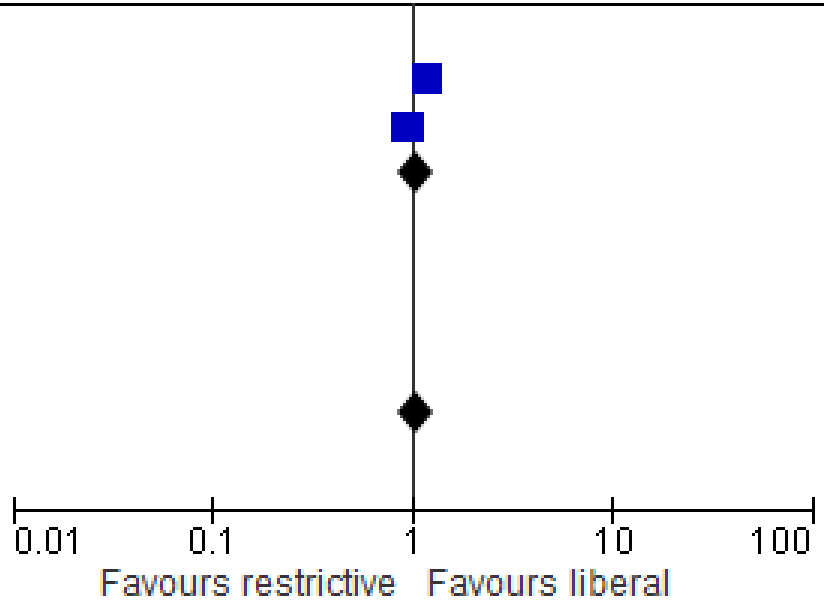


Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: 90-day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Septic shock						
Bergamin 2017	106	151	88	149	47.6%	1.19 [1.00, 1.41]
Holst 2014	216	502	223	496	52.4%	0.96 [0.83, 1.10]
Subtotal (95% CI)		**653**		**645**	**100.0%**	**1.06 [0.85, 1.32]**
Total events	322		311			
Heterogeneity: Tau² = 0.02; Chi² = 3.89, df = 1 (P = 0.05); I² = 74%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**653**		**645**	**100.0%**	**1.06 [0.85, 1.32]**
Total events	322		311			
Heterogeneity: Tau² = 0.02; Chi² = 3.89, df = 1 (P = 0.05); I² = 74%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Not applicable						

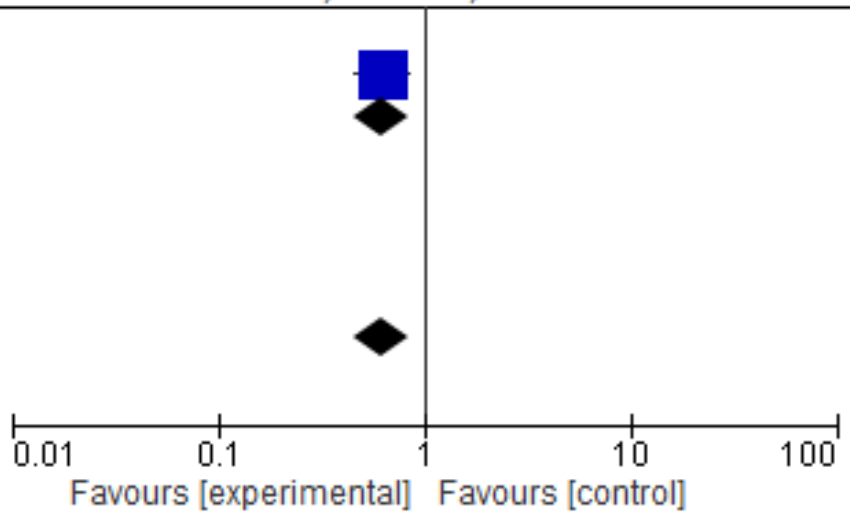


Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: cardiac events

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Critically ill, stable ICU						
Hébert 1999	55	418	88	420	100.0%	0.63 [0.46, 0.85]
Subtotal (95% CI)		**418**		**420**	**100.0%**	**0.63 [0.46, 0.85]**
Total events	55		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.96 (P = 0.003)						
Total (95% CI)		**418**		**420**	**100.0%**	**0.63 [0.46, 0.85]**
Total events	55		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.96 (P = 0.003)						
Test for subgroup differences: Not applicable						

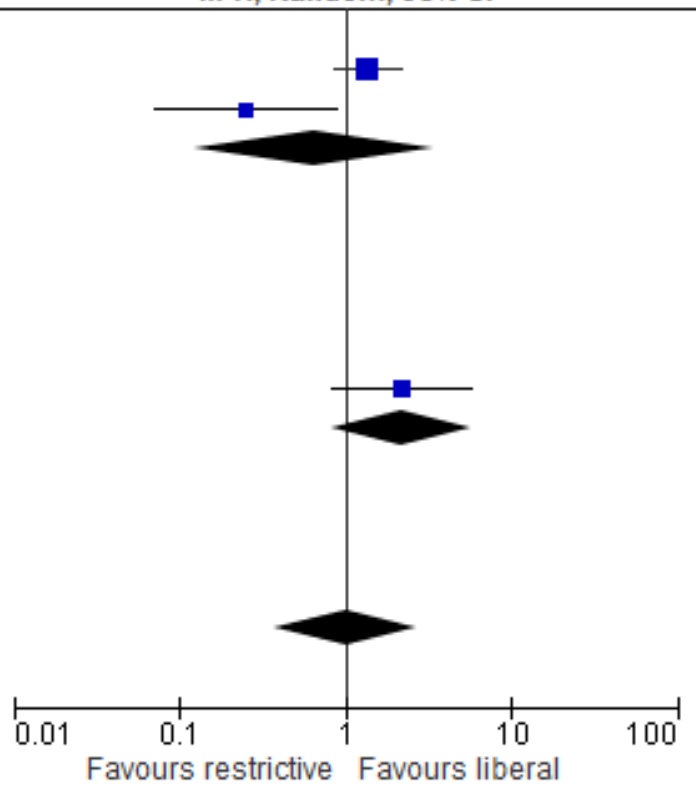


Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: myocardial infarction

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Critically ill, stable ICU						
Bergamin 2017	33	151	24	149	41.6%	1.36 [0.84, 2.18]
Hébert 1999	3	418	12	420	26.4%	0.25 [0.07, 0.88]
Subtotal (95% CI)		**569**		**569**	**67.9%**	**0.65 [0.12, 3.43]**
Total events	36		36			
Heterogeneity: Tau² = 1.24; Chi² = 6.26, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.7.2 Septic shock						
Holst 2014	13	488	6	489	32.1%	2.17 [0.83, 5.67]
Subtotal (95% CI)		**488**		**489**	**32.1%**	**2.17 [0.83, 5.67]**
Total events	13		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
Total (95% CI)		**1057**		**1058**	**100.0%**	**1.01 [0.38, 2.72]**
Total events	49		42			
Heterogeneity: Tau² = 0.55; Chi² = 7.75, df = 2 (P = 0.02); I² = 74%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.3%						

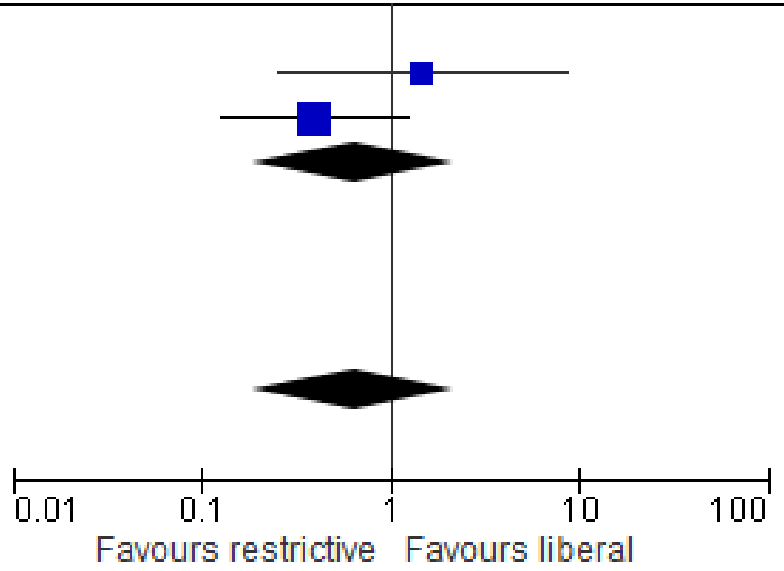


Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: CVA-stroke

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Septic shock						
Bergamin 2017	3	151	2	149	36.1%	1.48 [0.25, 8.73]
Holst 2014	4	488	10	489	63.9%	0.40 [0.13, 1.27]
Subtotal (95% CI)		**639**		**638**	**100.0%**	**0.64 [0.19, 2.20]**
Total events	7		12			
Heterogeneity: Tau² = 0.27; Chi² = 1.46, df = 1 (P = 0.23); I² = 32%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**639**		**638**	**100.0%**	**0.64 [0.19, 2.20]**
Total events	7		12			
Heterogeneity: Tau² = 0.27; Chi² = 1.46, df = 1 (P = 0.23); I² = 32%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						

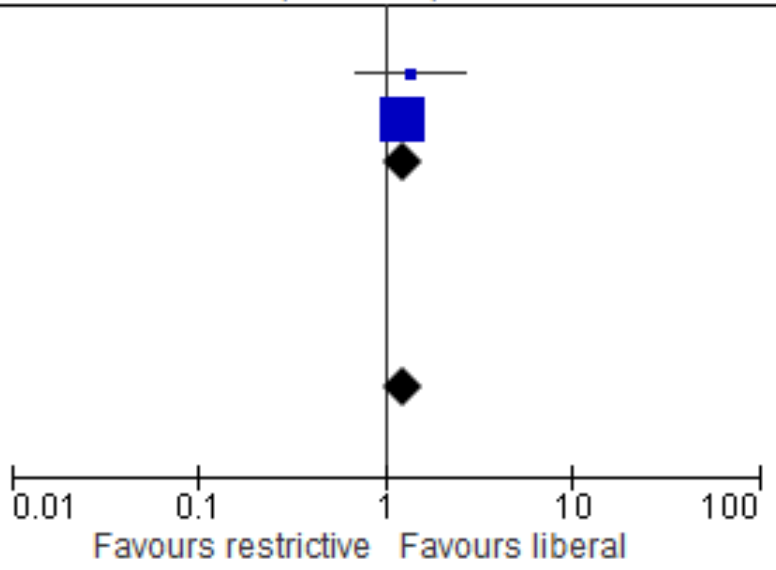


Acute intervention & intensive care

Critically ill, stable ICU + septic shock

CRITICAL OUTCOME: Renal failure

Study or Subgroup	Restrictive Events	Total	Liberal Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Septic shock						
Bergamin 2017	18	151	13	149	11.8%	1.37 [0.69, 2.69]
Holst 2014	109	432	88	429	88.2%	1.23 [0.96, 1.57]
Subtotal (95% CI)		**583**		**578**	**100.0%**	**1.25 [0.99, 1.57]**
Total events	127		101			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
Total (95% CI)		**583**		**578**	**100.0%**	**1.25 [0.99, 1.57]**
Total events	127		101			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
Test for subgroup differences: Not applicable						



Acute intervention & intensive care

Critically ill, stable ICU

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (< 7-8 g/dL) versus liberal (<9-10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
Participants exposed to blood transfusion	**302 fewer per 1.000** (349 fewer to 264 fewer)	**RR 0.68** (0.63 to 0.72)
Units of blood transfused	MD **3 units lower** (3.64 lower to 2.36 lower)	-
Haemoglobin concentration	MD **1.66 lower** (2.15 lower to 1.16 lower)	-
Congestive heart failure	**55 fewer per 1.000** (75 fewer to 21 fewer)	**RR 0.49** (0.30 to 0.80)
Sepsis-bacteraemia	**24 fewer per 1.000** (50 fewer to 18 more)	**RR 0.75** (0.48 to 1.19)
Pneumonia or wound infection	**19 fewer per 1.000** (51 fewer to 29 more)	**RR 0.84** (0.57 to 1.24)
Number of RBC transfusions	median **8 RBC transfusions lower** (0 to 0)	-

Undesirable effects?

Outcomes	Difference (restrictive (< 7-8 g/dL) versus liberal (<9-10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
Pneumonia	**7 more per 1.000** (36 fewer to 61 more)	**RR 1.03** (0.84 to 1.27)
Blood stream infections	**0 fewer per 1.000** (74 fewer to 109 more)	**RR 1.00** (0.69 to 1.46)
Wound infections	**0 fewer per 1.000** (52 fewer to 93 more)	**RR 1.00** (0.56 to 1.78)
Urinary tract infection	**7 more per 1.000** (52 fewer to 106 more)	**RR 1.05** (0.62 to 1.78)

Acute intervention & intensive care

Septic shock

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference restrictive (<7 g/dL) versus liberal (<9 g/dL) RBC transfusion triggers	Relative effect (95% CI)
1-year mortality	**11 fewer per 1.000** (71 fewer to 55 more)	**RR 0.98** (0.87 to 1.10)
Mortality at the time of longest follow-up	**43 fewer per 1.000** (98 fewer to 18 more)	**RR 0.93** (0.84 to 1.03)
Patients exposed to RBC transfusion	**306 fewer per 1.000** (342 fewer to 270 fewer)	**RR 0.66** (0.62 to 0.70)
Haemoglobin concentration	MD **1.7 lower** (1.82 lower to 1.58 lower)	-
Danish short form health survey questionnaire (SF-36): physical component summary score	MD **0.4 points higher** (4.05 lower to 4.85 higher)	-
Danish short form health survey questionnaire (SF-36): mental component summary score	MD **0.5 points higher** (5.26 lower to 6.26 higher)	-

Undesirable effects?

NONE

Acute intervention & intensive care

Quality of the body of evidence (critical outcomes)?

Critically ill, stable ICU

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕⊕⊕◯ MODERATE[a]
Hospital mortality	⊕⊕⊕◯ MODERATE[a]
Cardiac events	⊕⊕◯◯ LOW[b,c]
Myocardial infarction	⊕⊕⊕◯ MODERATE[a]
30-day mortality (subgroup: less severe patients (APACHE-score 20 or less))	⊕⊕◯◯ LOW[b,c]
30-day mortality (subgroup: cardiac disease)	⊕⊕◯◯ LOW[a,b]
30-day mortality (subgroup: severe infections and septic shock)	⊕⊕◯◯ LOW[a,b]

a. Imprecision: low number of events and/or large variability of the results
b. Risk of bias: detection bias (lack of blinding outcome assessors)
c. Indirectness: lack of generaliziblity: evidence from 1 Canadian study

Septic shock

Outcomes	Certainty of the evidence (GRADE)
28-30-day mortality	⊕⊕⊕◯ MODERATE[a]
Hospital mortality	⊕⊕⊕◯ MODERATE[b]
90-day mortality	⊕⊕⊕◯ MODERATE[a]
Myocardial infarction	⊕⊕⊕◯ MODERATE[a]
CVA-stroke	⊕⊕⊕◯ MODERATE[a]
60-day mortality	⊕⊕◯◯ LOW[a,c]

a. Imprecision: Large variability in results
b. Indirectness: Lack of generalizibility: evidence from 1 study conducted in Denmark
c. Indirectness: Lack of generalizibility: evidence from 1 study conducted in Brazil

Acute interventions & intensive care

Orthopaedic and non-cardiac surgery
Cardiac surgery
Coronary heart disease

Jerrold Levy

Study characteristics

Orthopaedic and non-cardiac surgery

Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Bush, 1997, USA	RCT	99 participants undergoing elective aortic or infrainguinal arterial reconstruction	RBC transfusion if Hb <9.0 g/dL	Hb maintained ≥10.0 g/dL
Carson, 1998, USA	RCT	84 hip fracture participants (in USA and Scotland) undergoing surgical repair with postoperative Hb<10.0 g/dL	Transfusion permitted if symptoms of anemia or Hb<8g/dL; 1 unit at a time until symptoms disappeared or Hb increased >8 g/dL	Immediately transfuse 1 unit after randomisation (Hb<10 g/dL) and transfuse enough blood to maintain Hb>10 g/dL
Carson, 2011, USA	RCT	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	Transfusion permitted if symptoms of anaemia or Hb<8g/dL; 1 unit at a time until symptoms disappeared or Hb increased >8 g/dL	Immediately transfuse 1 unit after randomisation (Hb<10 g/dL) and transfuse enough blood to maintain Hb>10 g/dL
Fan, 2014, China	RCT	186 participants (>65 years) undergoing elective unilateral total hip replacement	Transfusion if symptoms of anemia or Hb<8g/dL	Transfuse enough blood to maintain Hb>10 g/dL
Foss, 2009, Denmark	RCT	120 hip fracture participants (>65 years)	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)	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)
Gregersen, 2015, Denmark	RCT	284 participants (≥65 years) undergoing hip fracture surgery with postoperative 9.7 g/dL<Hb 11.3 g/dL	Transfusion if Hb<9.7 g/dL until target achieved with max 2 units per day	Transfusion if Hb<11.3 g/dL until target achieved with max 2 units per day
Grover, 2006, UK	RCT	260 participants undergoing elective lower limb joint replacement surgery	Transfusion if Hb<8.0 g/dL, Hb conc maintained at 8.0-9.5 g/dL	Transfusion if Hb<10.0 g/dL, Hb conc maintained at 10.0-12.0 g/dL
Lotke, 1999, USA	RCT	152 participants undergoing primary total knee arthroplasty (TKA)	Transfusion of the 2 units of autologous blood if Hb <9.0 g/dL	Transfusion of the 2 units of autologous blood immediately after surgery in the recovery room
Markatou, 2012, Greece	RCT	52 participants scheduled for elective upper major abdominal surgery	Transfusion if Hb <7.7 g/dL, target Hb 7.7-9.9 g/dL	Transfusion if Hb <9.9 g/dL, target Hb >10 g/dL
Nielsen, 2014, Denmark	RCT	66 participants (>18 years) scheduled for elective hip revision surgery	Transfusion if Hb<7.3 g/dL with target range of 7.3-8.9 g/dL	Transfusion if Hb<8.9 g/dL with target >8.9 g/dL
Parker, 2013, UK	RCT	200 participants (>60 years) with hip fracture, 8.0 g/dL<Hb<9.5 g/dL	Transfusion only if definite symptoms of anemia	Transfusion of at least 1 unit of blood and then maintained >10.0 g/dL
So-Osman, 2013, The Netherlands	RCT	603 participants in 3 hospitals undergoing elective orthopaedic surgery	According to new protocol hospital 1 and 2 and to the standard protocol in hospital 3 Hb threshold values were based on age and comorbidities, details are provided in Appendix paper So-Osman et al. (2013)	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)

Study characteristics

Cardiac surgery

Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Bracey, 1999, USA	RCT	428 consecutive participants undergoing elective primary coronary artery bypass graft surgery	Transfusion in the postoperative period at a Hb level <8.0 g/dL	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
Hajjar, 2010, Brazil	RCT	502 adult participants who underwent cardiac surgery with cardiopulmonary bypass	Transfusion if haematocrit <24% (~Hb level <8 g/dL)	Transfusion if haematocrit <30% (~Hb level <10 g/dL)
Johnson, 1992, USA	RCT	39 autologous blood donors undergoing elective myocardial revascularisation	Transfusion if post-operative haematocrit <25% (~Hb level <8.33 g/dL)	Transfusion to achieve post-operative haematocrit of 32% (~Hb level <10.67 g/dL)
Koch, 2017, USA	RCT	717 adults undergoing CABG surgery or valve procedures	Transfusion if haematocrit <24% (= +/- 8 g/dL)	Transfusion if haematocrit <28% (= +/- 9.3 g/dL)
Laine, 2017, Finland	RCT	80 patients scheduled for non-emergency coronary artery bypass grafting simple one valve (aortic or mitral) replacement or both, requiring cardiopulmonary bypass	Transfusion if Hb <8.0 g/dL until above this threshold	Transfusion if Hb <10.0 g/dL until above this threshold
Mazer, 2017, Canada	RCT	Participants (from 19 countries across the world) older than 18 years of age scheduled to undergo cardiac surgery with cardiopulmonary bypass	Transfusion if Hb <7.5 g/dL intraoperatively or postoperatively	Transfusion if Hb <9.5 g/dL intraoperatively or postoperatively in ICU or if Hb <8.5 g/dL in non-ICU ward
Murphy, 2015, UK	RCT	Participants older than 16 years of age who were undergoing nonemergency cardiac surgery	Transfusion if post-surgery Hb level <7.5 g/dL	Transfusion if post-surgery Hb level <9.0 g/dL
Shehata, 2012, Canada	RCT	50 adult participants undergoing cardiac surgery	RBC transfusions if Hb ≤7.0 g/dL during cardiopulmonary bypass and ≤7.5 g/dL postoperatively	RBC transfusions if Hb ≤ 9.5 g/dL during cardiopulmonary bypass and ≤10 g/dL postoperatively

Study characteristics

Coronary heart disease

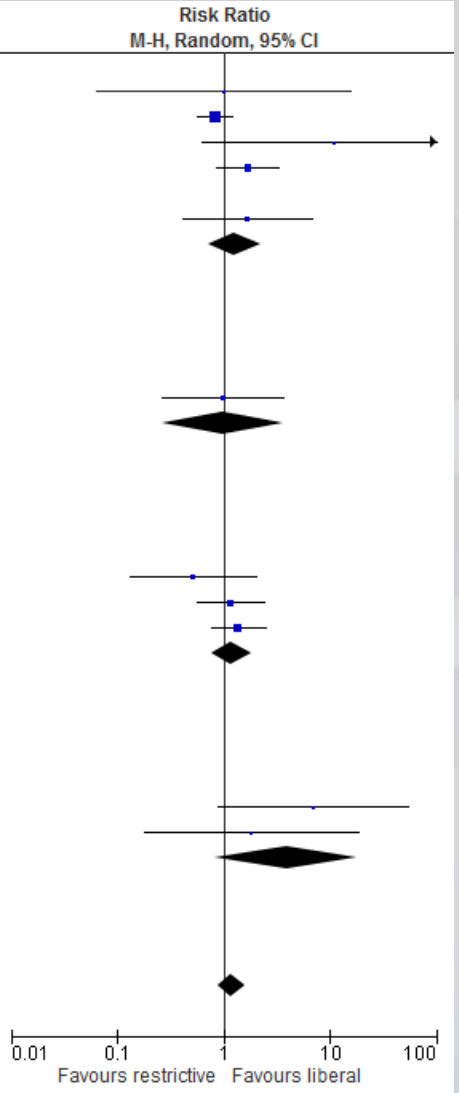
Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Carson, 2013, USA	RCT	110 participants with acute myocardial infarction or undergoing cardiac catheterisation	Restrictive group (intervention): transfusion permitted if symptoms of anemia or Hb<8 g/dL; 1 unit at a time until symptoms disappeared or Hb increased >8 g/dL	Immediately transfuse 1 unit after randomisation (Hb<10 g/dL) and transfuse enough blood to maintain Hb>10 g/dL
Cooper, 2011, USA	RCT	45 participants with acute myocardial infarction	Transfusion with RBC if haematocrit <24%; target haematocrit: 24-27% (Hb: 8-9 g/dL)	Transfusion with RBC if haematocrit <30%; target haematocrit: 30-33% (Hb: 10-11 g/dL)

Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

CRITICAL OUTCOME: 30-day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Orthopaedic surgery						
Carson 1998	1	42	1	42	1.2%	1.00 [0.06, 15.47]
Carson 2011	43	1009	52	1007	31.7%	0.83 [0.56, 1.22]
Foss 2009	5	60	0	60	1.1%	11.00 [0.62, 194.63]
Gregersen 2015	21	144	12	140	15.6%	1.70 [0.87, 3.32]
Lotke 1999	0	62	0	65		Not estimable
Parker 2013	5	100	3	100	4.3%	1.67 [0.41, 6.79]
Subtotal (95% CI)		**1417**		**1414**	**53.9%**	**1.27 [0.72, 2.25]**
Total events	75		68			
Heterogeneity: Tau² = 0.14; Chi² = 6.46, df = 4 (P = 0.17); I² = 38%						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.1.2 Vascular surgery						
Bush 1997	4	50	4	49	4.8%	0.98 [0.26, 3.70]
Subtotal (95% CI)		**50**		**49**	**4.8%**	**0.98 [0.26, 3.70]**
Total events	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.1.3 Cardiac surgery						
Bracey 1999	3	215	6	222	4.5%	0.52 [0.13, 2.04]
Hajjar 2010	15	249	13	253	13.9%	1.17 [0.57, 2.41]
Murphy 2015	26	1000	19	1003	19.2%	1.37 [0.76, 2.46]
Subtotal (95% CI)		**1464**		**1478**	**37.6%**	**1.18 [0.77, 1.81]**
Total events	44		38			
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.1.4 Coronary heart disease						
Carson 2013	7	55	1	55	2.1%	7.00 [0.89, 55.01]
Cooper 2011	2	23	1	21	1.6%	1.83 [0.18, 18.70]
Subtotal (95% CI)		**78**		**76**	**3.7%**	**3.88 [0.83, 18.13]**
Total events	9		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**3009**		**3017**	**100.0%**	**1.19 [0.88, 1.61]**
Total events	132		112			
Heterogeneity: Tau² = 0.03; Chi² = 11.57, df = 10 (P = 0.31); I² = 14%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Test for subgroup differences: Chi² = 2.27, df = 3 (P = 0.52), I² = 0%						



Acute intervention & intensive care

Cardiac surgery

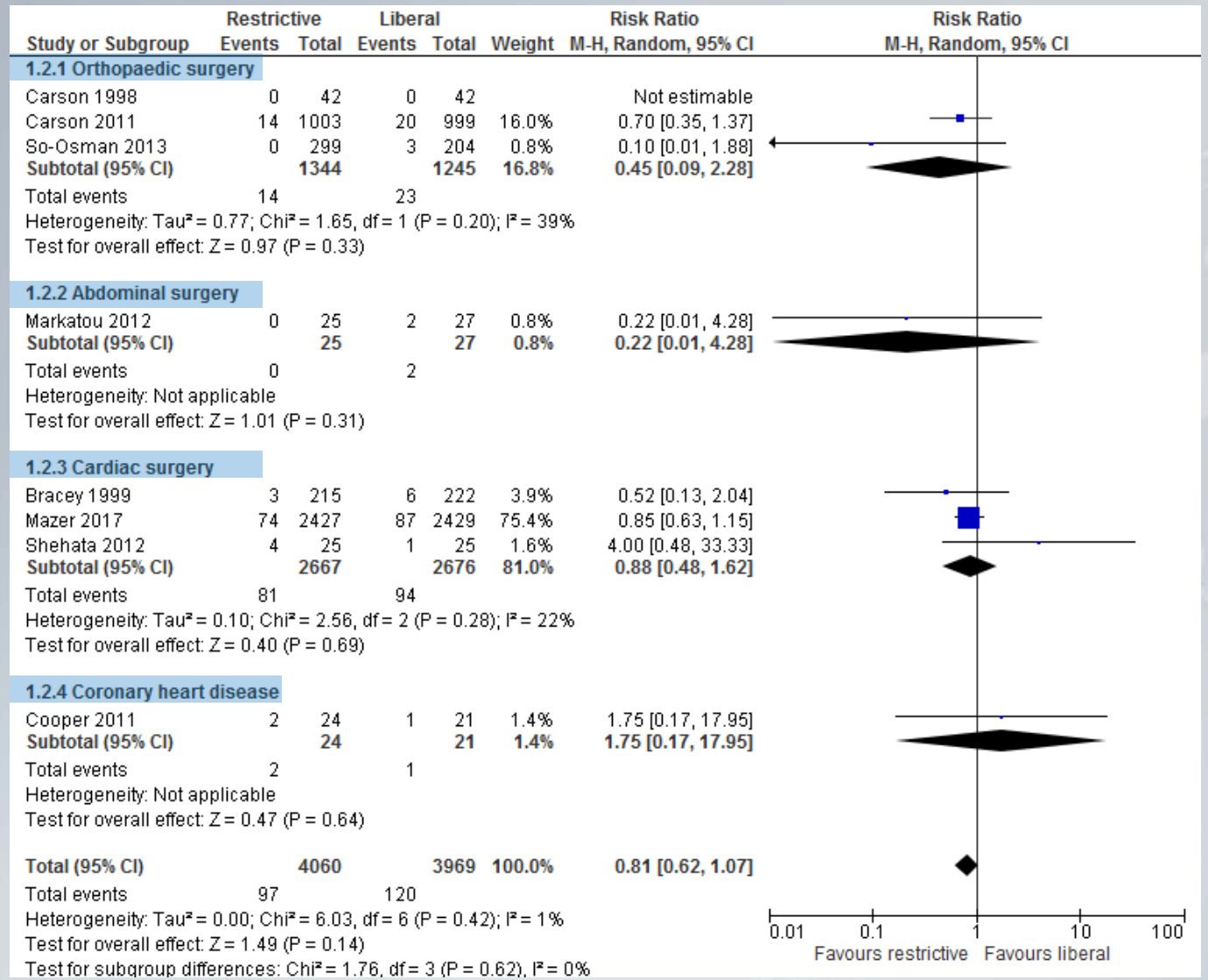
CRITICAL OUTCOME: 30-day mortality (subgroup analyses)

Outcomes	Difference (restrictive (< 7.5/8 g/dL) versus liberal (<9-10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
30-day mortality (subgroup: patients <60 years)	**2 fewer per 1.000** (31 fewer to 93 more)	**RR 0.95** (0.28 to 3.20)
30-day mortality (subgroup: patients ≥60 years)	**28 more per 1.000** (20 fewer to 152 more)	**RR 1.54** (0.61 to 3.93)
Renal failure (subgroup: patients <60 years)	**7 more per 1.000** (18 fewer to 116 more)	**RR 1.27** (0.29 to 5.55)
Renal failure (subgroup: patients ≥60 years)	**26 fewer per 1.000** (56 fewer to 54 more)	**RR 0.77** (0.24 to 1.73)

Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

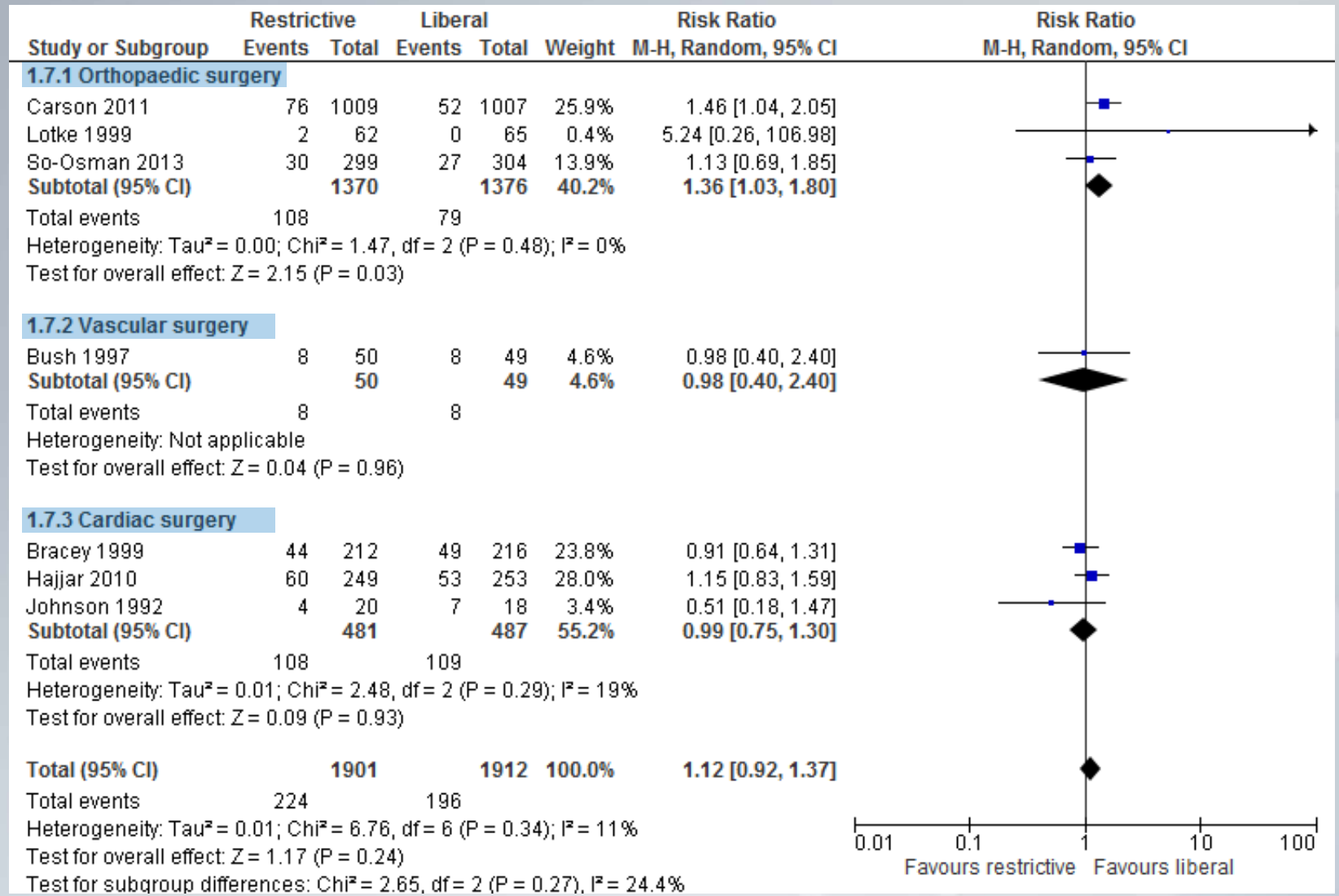
CRITICAL OUTCOME: hospital mortality



Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

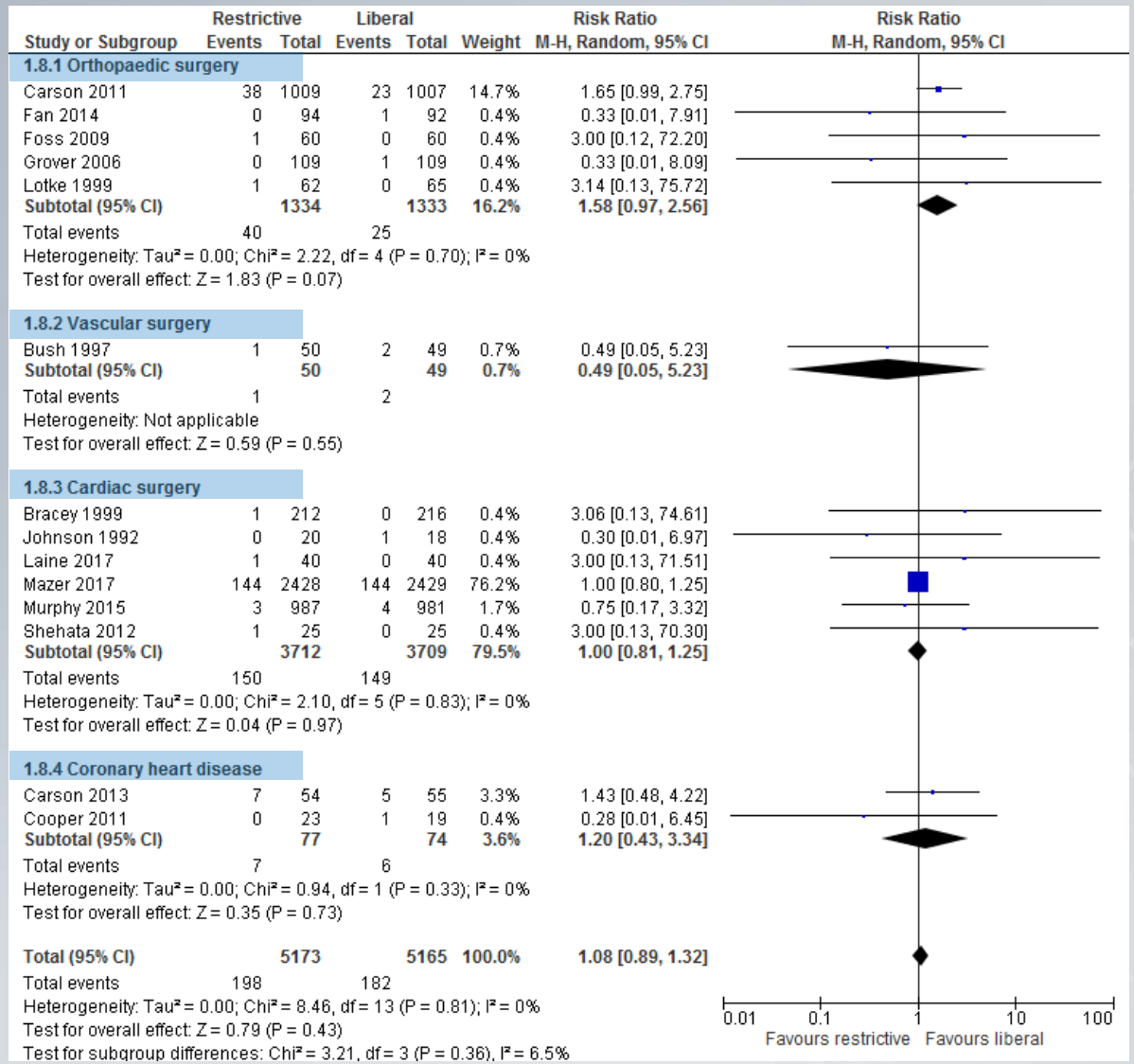
CRITICAL OUTCOME: cardiac events



‘Acute intervention & intensive care’

Orthopaedic & (non-)cardiac surgery and coronary heart disease

CRITICAL OUTCOME: myocardial infarction

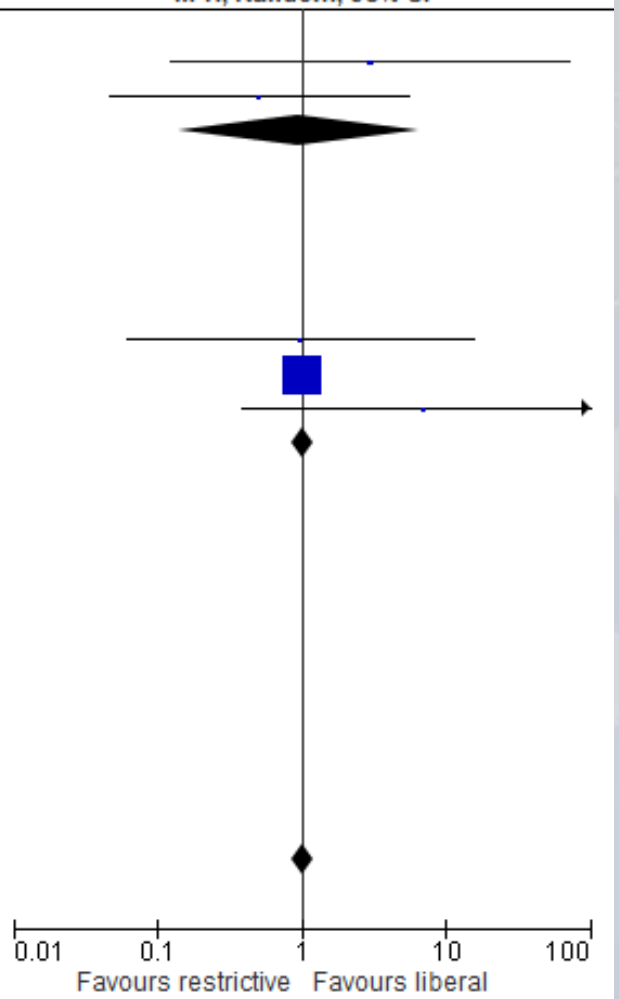


Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

CRITICAL OUTCOME: sepsis-bacteraemia

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Orthopaedic surgery						
Parker 2013	1	100	0	100	0.3%	3.00 [0.12, 72.77]
So-Osman 2013	1	299	2	304	0.5%	0.51 [0.05, 5.58]
Subtotal (95% CI)		**399**		**404**	**0.8%**	**0.96 [0.14, 6.55]**
Total events	2		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.11.2 Cardiac surgery						
Koch 2017	1	363	1	354	0.4%	0.98 [0.06, 15.53]
Murphy 2015	214	983	210	982	98.5%	1.02 [0.86, 1.20]
Shehata 2012	3	25	0	25	0.3%	7.00 [0.38, 128.87]
Subtotal (95% CI)		**1371**		**1361**	**99.2%**	**1.02 [0.87, 1.21]**
Total events	218		211			
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.11.3 Coronary heart disease						
Carson 2013	0	54	0	55		Not estimable
Subtotal (95% CI)		**54**		**55**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1824**		**1820**	**100.0%**	**1.02 [0.87, 1.21]**
Total events	220		213			
Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 4 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						

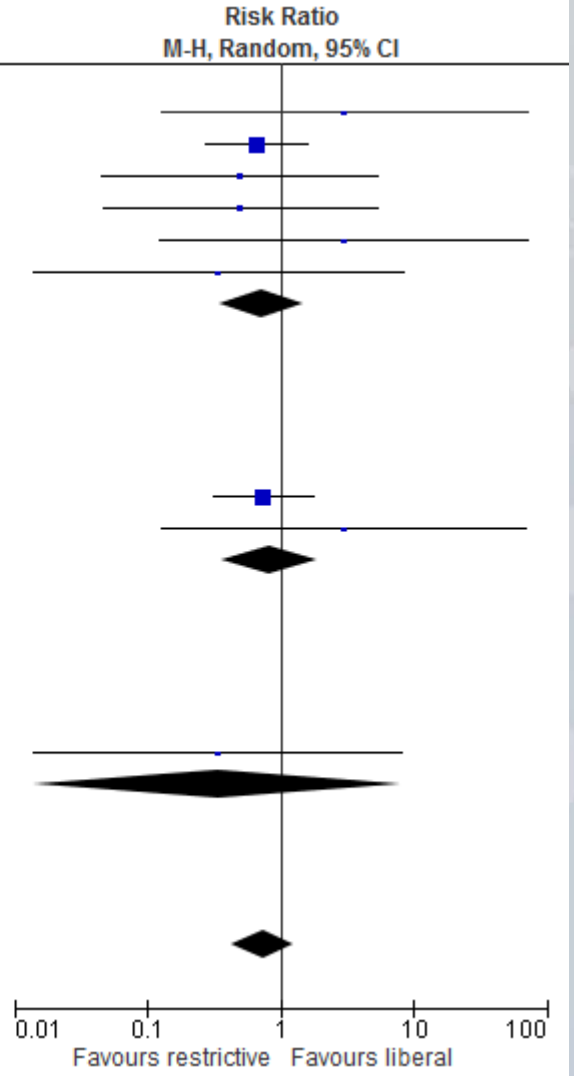


Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

CRITICAL OUTCOME: thromboembolism

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Orthopaedic surgery						
Carson 1998	1	42	0	42	2.9%	3.00 [0.13, 71.61]
Carson 2011	8	1009	12	1007	36.4%	0.67 [0.27, 1.62]
Fan 2014	1	94	2	92	5.1%	0.49 [0.05, 5.30]
Foss 2009	1	60	2	60	5.1%	0.50 [0.05, 5.37]
Parker 2013	1	100	0	100	2.8%	3.00 [0.12, 72.77]
So-Osman 2013	0	299	1	304	2.8%	0.34 [0.01, 8.29]
Subtotal (95% CI)		**1604**		**1605**	**55.2%**	**0.71 [0.34, 1.47]**
Total events	12		17			
Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 5 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.14.2 Cardiac surgery						
Murphy 2015	9	985	12	981	39.1%	0.75 [0.32, 1.76]
Shehata 2012	1	25	0	25	2.9%	3.00 [0.13, 70.30]
Subtotal (95% CI)		**1010**		**1006**	**42.0%**	**0.82 [0.36, 1.88]**
Total events	10		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
1.14.3 Coronary heart disease						
Carson 2013	0	54	1	55	2.9%	0.34 [0.01, 8.15]
Subtotal (95% CI)		**54**		**55**	**2.9%**	**0.34 [0.01, 8.15]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.51)						
Total (95% CI)		**2668**		**2666**	**100.0%**	**0.74 [0.43, 1.27]**
Total events	22		30			
Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 8 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Chi² = 0.30, df = 2 (P = 0.86), I² = 0%						

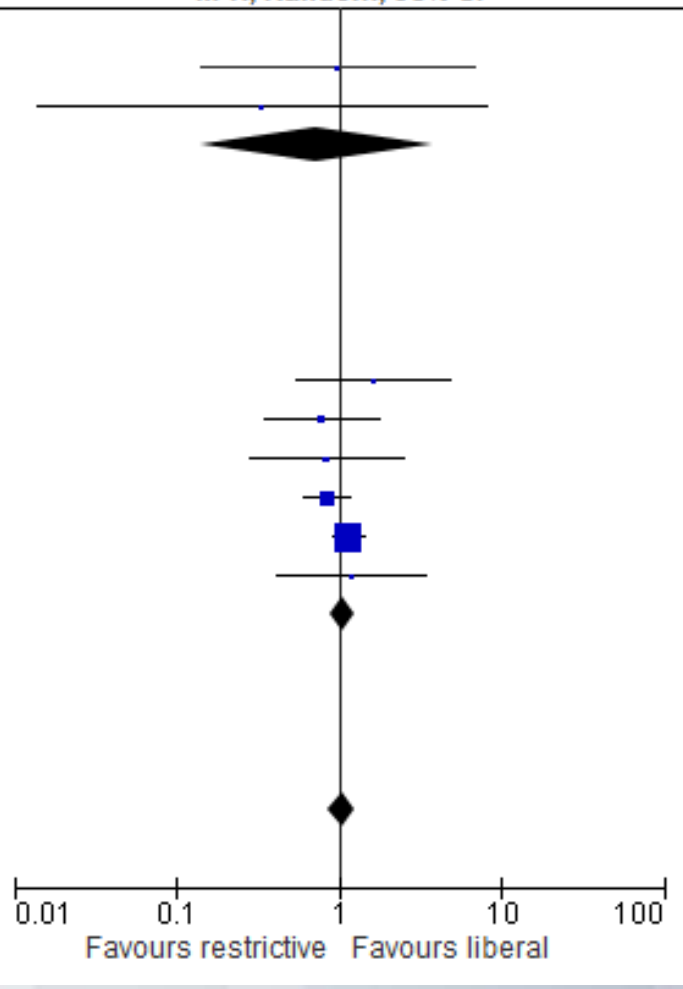


Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

CRITICAL OUTCOME: renal failure

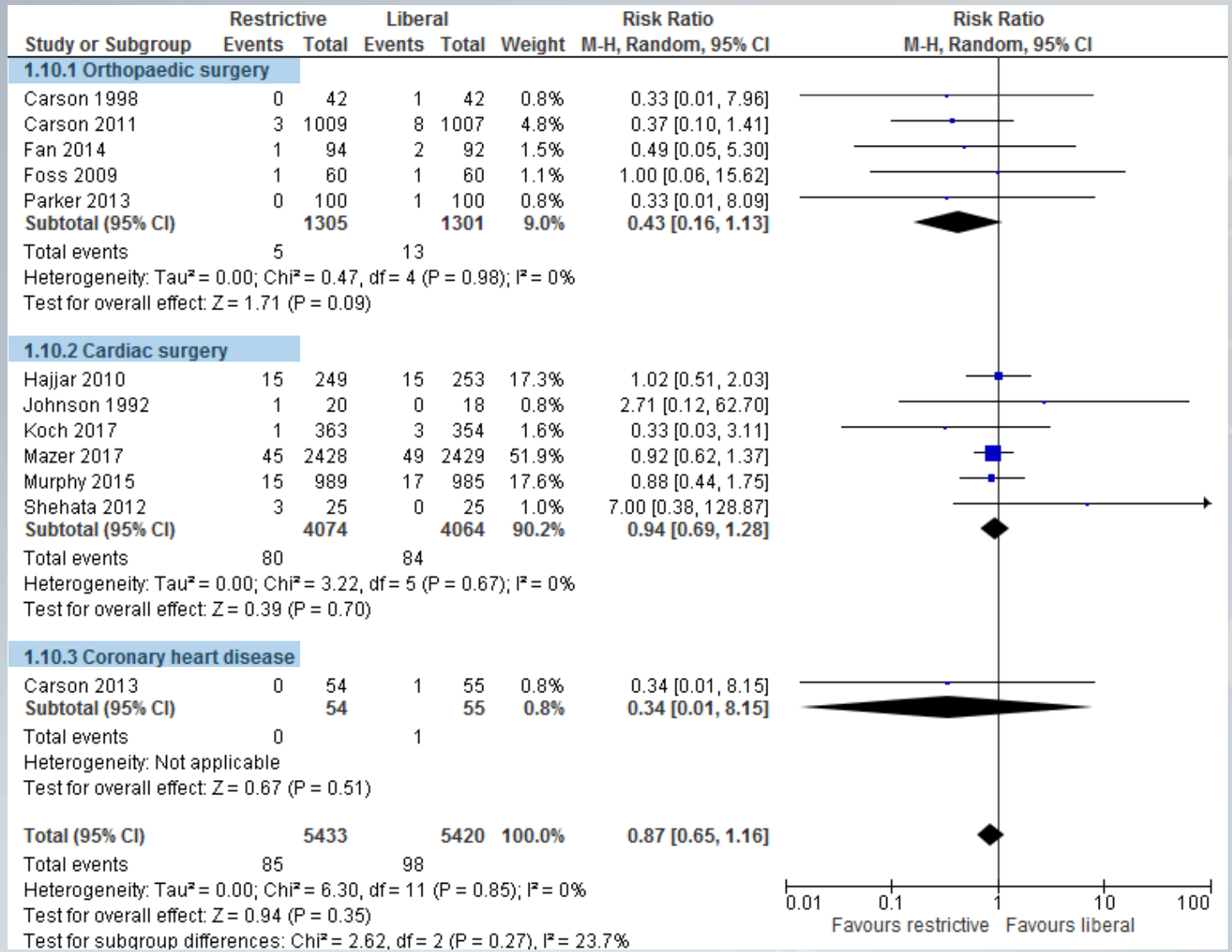
Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Orthopaedic surgery						
Fan 2014	2	94	2	92	0.8%	0.98 [0.14, 6.80]
Parker 2013	0	100	1	100	0.3%	0.33 [0.01, 8.09]
Subtotal (95% CI)		**194**		**192**	**1.1%**	**0.73 [0.14, 3.84]**
Total events	2		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.15.2 Cardiac surgery						
Bracey 1999	8	212	5	216	2.5%	1.63 [0.54, 4.90]
Hajjar 2010	10	249	13	253	4.7%	0.78 [0.35, 1.75]
Koch 2017	6	363	7	354	2.6%	0.84 [0.28, 2.46]
Mazer 2017	61	2428	72	2429	26.9%	0.85 [0.61, 1.19]
Murphy 2015	140	989	122	989	59.5%	1.15 [0.92, 1.44]
Shehata 2012	6	25	5	25	2.8%	1.20 [0.42, 3.43]
Subtotal (95% CI)		**4266**		**4266**	**98.9%**	**1.04 [0.87, 1.24]**
Total events	231		224			
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.66)						
Total (95% CI)		**4460**		**4458**	**100.0%**	**1.04 [0.87, 1.23]**
Total events	233		227			
Heterogeneity: Tau² = 0.00; Chi² = 4.00, df = 7 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.69)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

CRITICAL OUTCOME: CVA-stroke

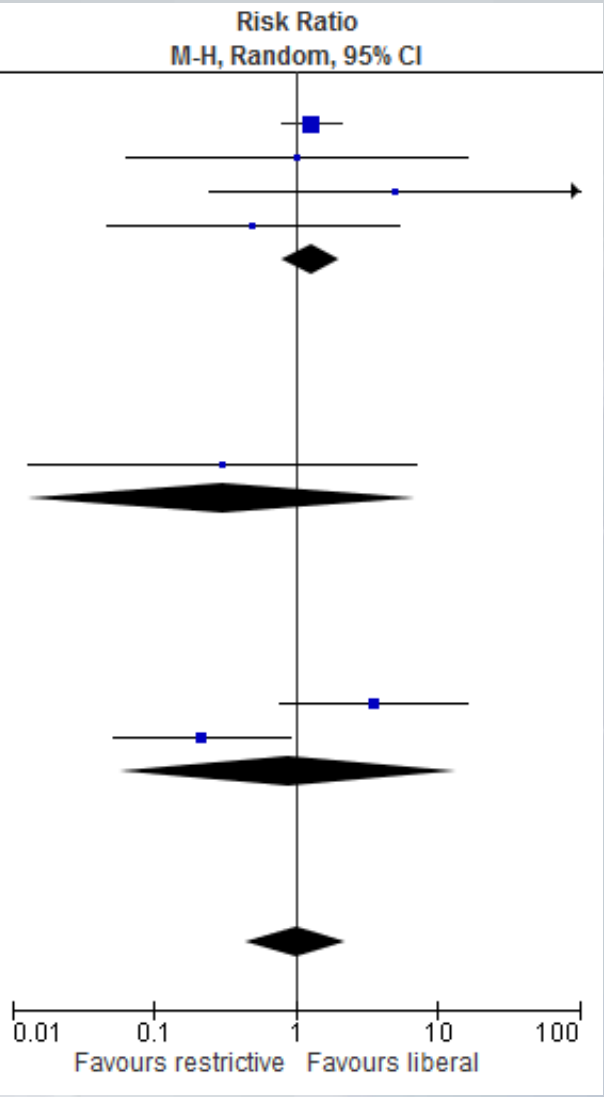


Acute intervention & intensive care

Orthopaedic & (non-)cardiac surgery and coronary heart disease

CRITICAL OUTCOME: congestive heart failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Orthopaedic surgery						
Carson 2011	35	1009	27	1007	37.3%	1.29 [0.79, 2.12]
Fan 2014	1	94	1	96	7.1%	1.02 [0.06, 16.09]
Foss 2009	2	60	0	60	6.1%	5.00 [0.25, 102.00]
Parker 2013	1	100	2	100	9.0%	0.50 [0.05, 5.43]
Subtotal (95% CI)		**1263**		**1263**	**59.3%**	**1.28 [0.80, 2.05]**
Total events	39		30			
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.9.2 Cardiac surgery						
Johnson 1992	0	20	1	18	5.7%	0.30 [0.01, 6.97]
Subtotal (95% CI)		**20**		**18**	**5.7%**	**0.30 [0.01, 6.97]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
1.9.3 Coronary heart disease						
Carson 2013	7	54	2	55	16.9%	3.56 [0.78, 16.40]
Cooper 2011	2	24	8	21	18.1%	0.22 [0.05, 0.92]
Subtotal (95% CI)		**78**		**76**	**35.0%**	**0.87 [0.06, 13.46]**
Total events	9		10			
Heterogeneity: Tau² = 3.33; Chi² = 6.83, df = 1 (P = 0.009); I² = 85%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**1361**		**1357**	**100.0%**	**1.00 [0.45, 2.24]**
Total events	48		41			
Heterogeneity: Tau² = 0.38; Chi² = 9.56, df = 6 (P = 0.14); I² = 37%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Chi² = 0.86, df = 2 (P = 0.65), I² = 0%						



Acute intervention & intensive care

Orthopaedic surgery and non-cardiac surgery

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference restrictive (<8-9 g/dL) versus liberal (<10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
Patients exposed to RBC transfusion	**408 fewer per 1.000** (506 fewer to 269 fewer)	**RR 0.50** (0.38 to 0.67)
RBC units transfused	MD **0.23 units lower** (0.85 lower to 0.39 higher)	-
Haemoglobin concentration	MD **0.99 lower** (1.53 lower to 0.45 lower)	-
Sepsis-bacteraemia	**0 fewer per 1.000** (4 fewer to 27 more)	**RR 0.96** (0.14 to 6.55)
Pneumonia	**10 fewer per 1.000** (22 fewer to 5 more)	**RR 0.83** (0.63 to 1.09)
Pneumonia or wound infection	**33 fewer per 1.000** (69 fewer to 22 more)	**RR 0.76** (0.50 to 1.16)
Mental confusion	**8 fewer per 1.000** (34 fewer to 29 more)	**RR 0.92** (0.65 to 1.30)

Undesirable effects?

Outcomes	Difference restrictive (<8-9 g/dL) versus liberal (<10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
Congestive heart failure	**7 more per 1.000** (5 fewer to 25 more)	**RR 1.28** (0.80 to 2.05)

Acute intervention & intensive care

Cardiac surgery

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (<7,5/8 g/dL) versus liberal (<9-10 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Patients exposed to RBC transfusion	**240 fewer per 1.000** (263 fewer to 209 fewer)	**RR 0.69** (0.66 to 0.73)
RBC units transfused (mean)	MD **0.87 units lower** (1.29 lower to 0.45 lower)	-
Haemoglobin concentration	MD **1.4 lower** (3.1 lower to 0.3 higher)	-
Rebleeding	**3 fewer per 1.000** (11 fewer to 11 more)	**RR 0.87** (0.51 to 1.48)
Health-related quality of life EQ-5D at 6 weeks	MD **0.01 points higher** (0.02 lower to 0.03 higher)	-
Vascular morbidity (aortic or femoral artery dissection or acute limb ischaemia)	**7 fewer per 1.000** (8 fewer to 14 more)	**RR 0.14** (0.01 to 2.69)
Reoperative morbidity (for bleeding/tamponade, graft occlusion, valve dysfunction)	**3 fewer per 1.000** (18 fewer to 32 more)	**RR 0.88** (0.36 to 2.13)

Undesirable effects?

Outcomes	Difference (restrictive (<7,5/8 g/dL) versus liberal (<9-10 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Pneumonia or wound infection	**7 more per 1.000** (6 fewer to 21 more)	**RR 1.07** (0.94 to 1.22)
Health-related quality of life EQ-5D at 3 months	MD **0 points** (0.03 lower to 0.02 higher)	-
Pulmonary morbidity (pneumonia, pulmonary embolus or prolonged postoperative ventilation >24 hours)	**10 more per 1.000** (19 fewer to 61 more)	**RR 1.18** (0.65 to 2.13)
Gastrointestinal morbidity	**8 more per 1.000** (3 fewer to 65 more)	**RR 2.44** (0.48 to 12.48)

Acute intervention & intensive care

Coronary heart disease

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference Difference restrictive (<8 g/dL) versus liberal (<10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
Participants exposed to RBC transfusion	**600 fewer per 1.000** (810 fewer to 180 fewer)	**RR 0.40** (0.19 to 0.82)
RBC units transfused	MD **0.9 units lower** (1.87 lower to 0.07 higher)	-
Haemoglobin concentration	MD **1.52 lower** (1.79 lower to 1.25 lower)	-

Undesirable effects?

Outcomes	Difference Difference restrictive (<8 g/dL) versus liberal (<10 g/dL) RBC transfusion triggers	Relative effect (95% CI)
Pneumonia	**0 fewer per 1.000** (0 fewer to 0 fewer)	**RR 5.09** (0.25 to 103.64)
Pneumonia or wound infection	**0 fewer per 1.000** (0 fewer to 0 fewer)	**RR 5.09** (0.25 to 103.64)

Acute intervention & intensive care

Orthopaedic surgery and non-cardiac surgery

Quality of the body of evidence (critical outcomes)?

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕⊕⊕◯ MODERATE[a]
Hospital mortality	⊕⊕◯◯ LOW[a,d]
90-day mortality	⊕⊕◯◯ LOW[a,g]
Cardiac events	⊕⊕⊕⊕ HIGH
Myocardial infarction	⊕⊕⊕◯ MODERATE[a]
CVA-stroke	⊕⊕◯◯ LOW[a,d]
Thromboembolism	⊕⊕⊕◯ MODERATE[a]
Renal failure	⊕⊕◯◯ LOW[a,h]
Inability to walk or death at 30/60 days	⊕⊕⊕◯ MODERATE[c]

a. Imprecision: large variability in results
b. Risk of bias: selection bias (randomization + allocation concealment unclear), performance bias (lack of blinding unclear), reporting bias (no pre-registration study protocol).
c. Indirectness: lack of generalizibility: Single centre study conducted in the USA
d. Risk of bias: detection bias and reporting bias
e. Indirectness: lack of generalizibility: Single centre study conducted in Greece
f. Imprecision: low number of events, limited sample size and/or large variability in results
g. Indirectness: lack of generaliziblity: 2 small single centre studies form UK and Denmark
h. Risk of bias: detection bias and selection bias

Acute intervention & intensive care

Cardiac surgery

Quality of the body of evidence (critical outcomes)?

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕⊕⊕◯ MODERATE[a]
30-day mortality (subgroup: patients <60 years)	⊕⊕◯◯ LOW[b]
30-day mortality (subgroup: patients ≥60 years)	⊕⊕◯◯ LOW[b]
Hospital mortality	⊕⊕⊕◯ MODERATE[a]
Cardiac events	⊕⊕◯◯ LOW[c,d]
Myocardial infarction	⊕⊕⊕◯ MODERATE[d]
CVA-stroke	⊕⊕◯◯ LOW[a,d]
Renal failure	⊕⊕⊕◯ MODERATE[d]
Renal failure (subgroup: patients <60 years)	⊕⊕◯◯ LOW[d]
Renal failure (subgroup: patients ≥60 years)	⊕⊕◯◯ LOW[b,d]

a. Imprecision: Low number of events, limited sample size and/or large variability in results
b. Indirectness: Lack of generalizibility: evidence from 1 Brazilian study
c. Risk of bias: Selection bias and detection bias
d. Indirectness: Lack of generazibility: variation in outcome definitions

Acute intervention & intensive care

Coronary heart disease

Quality of the body of evidence (critical outcomes)?

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⨁⨁◯◯ LOW[a]
Hospital mortality	⨁⨁◯◯ LOW[a]
Myocardial infarction	⨁⨁◯◯ LOW[a]
Congestive heart failure	⨁◯◯◯ VERY LOW[a,b]
CVA-stroke	⨁⨁◯◯ LOW[a]
Thromboembolism	⨁⨁◯◯ LOW[a]

a. Imprecision: Low number of events, limited sample size and/or large variability in results
b. Inconsistency: Decision to downgrade by reviewer(s) since point estimates vary, CIs show minimal overlap, test for heterogeneity shows a low p-value and I^2>75%. Moreover, the point estimates point to different directions of effect.

Acute interventions & intensive care

Acute gastrointestinal bleeding
Acute bleeding

Cécile Aubron

Study characteristics

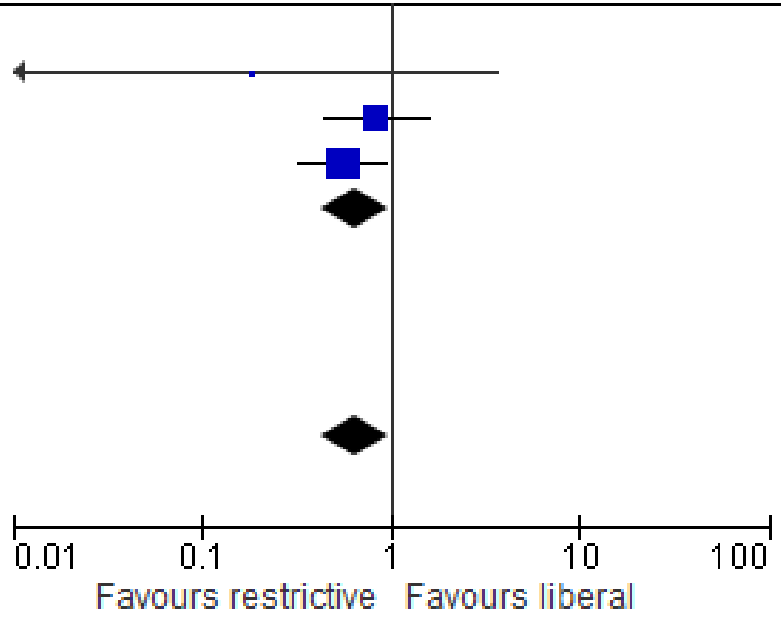
Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Blair, 1986, UK	RCT	50 consecutive participants with severe upper gastrointestinal haemorrhage	Not transfused unless the Hb <8.0 g/dL or shock persisted after initial resuscitation	At least 2 units of red blood cells during their first 24 hours in hospital
Fisher, 1956, United Kingdom	RCT	22 trauma participants	An attempt was made to leave the RBC volume at the end of resuscitation at 70% to 80% of normal.	To achieve 100% or more of the RBC volume at the end of resuscitation.
Jairath, 2015, UK	RCT	936 participants with upper gastrointestinal bleeding in 6 hospitals	Transfusion if Hb<8 g/dL, post-transfusion target of 8.1–10.0 g/dL	Transfusion if Hb<10 g/dL threshold, post-transfusion Hb target of 10.1–12.0 g/dL
Villanueva, 2013, Spain	RCT	889 participants with haematemesis and/or melena due to upper GI bleeding	Transfusion if Hb<7 g/dL target range for the post-transfusion Hb level of 7-9 g/dL	Transfusion if Hb<9 g/dL target range for the post-transfusion Hb level of 9-11 g/dL

Acute intervention & intensive care

Acute (gastrointestinal) bleeding

CRITICAL OUTCOME: 30-day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Acute gastrointestinal bleeding						
Blair 1986	0	26	2	24	1.9%	0.19 [0.01, 3.67]
Jairath 2015	14	257	25	382	41.6%	0.83 [0.44, 1.57]
Villanueva 2013	19	416	34	417	56.5%	0.56 [0.32, 0.97]
Subtotal (95% CI)		**699**		**823**	**100.0%**	**0.65 [0.43, 0.97]**
Total events	33		61			
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
Total (95% CI)		**699**		**823**	**100.0%**	**0.65 [0.43, 0.97]**
Total events	33		61			
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
Test for subgroup differences: Not applicable						



Acute intervention & intensive care

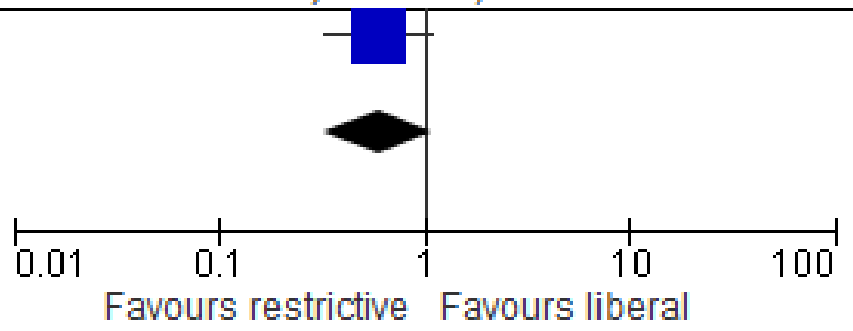
Acute gastrointestinal bleeding

CRITICAL OUTCOME: 30-day mortality (subgroup analyses: patients with cirrhosis)

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Villanueva 2013	15	139	25	138	100.0%	0.60 [0.33, 1.08]
Total (95% CI)		**139**		**138**	**100.0%**	**0.60 [0.33, 1.08]**
Total events	15		25			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.71 (P = 0.09)

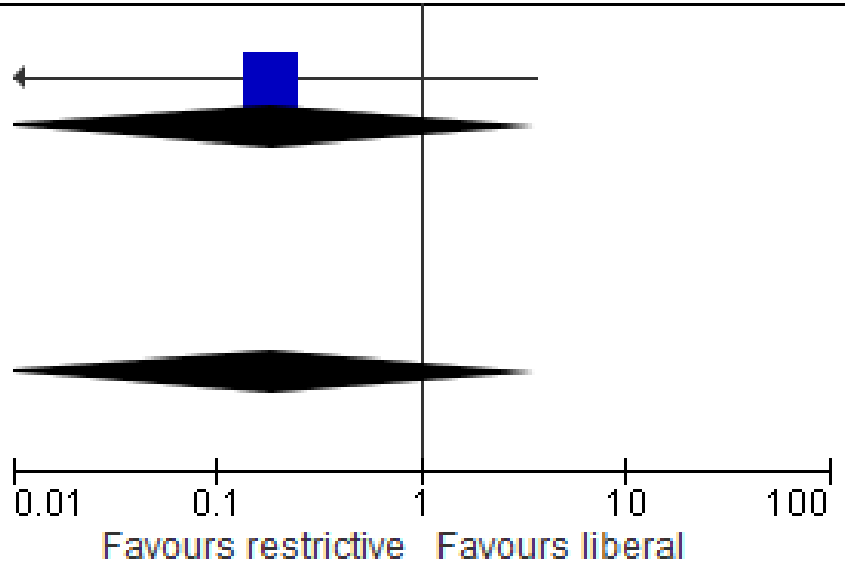


Acute intervention & intensive care

Acute (gastrointestinal) bleeding

CRITICAL OUTCOME: hospital mortality

Study or Subgroup	Restrictive Events	Total	Liberal Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Acute gastrointestinal bleeding						
Blair 1986	0	26	2	24	100.0%	0.19 [0.01, 3.67]
Subtotal (95% CI)		**26**		**24**	**100.0%**	**0.19 [0.01, 3.67]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**26**		**24**	**100.0%**	**0.19 [0.01, 3.67]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Test for subgroup differences: Not applicable						

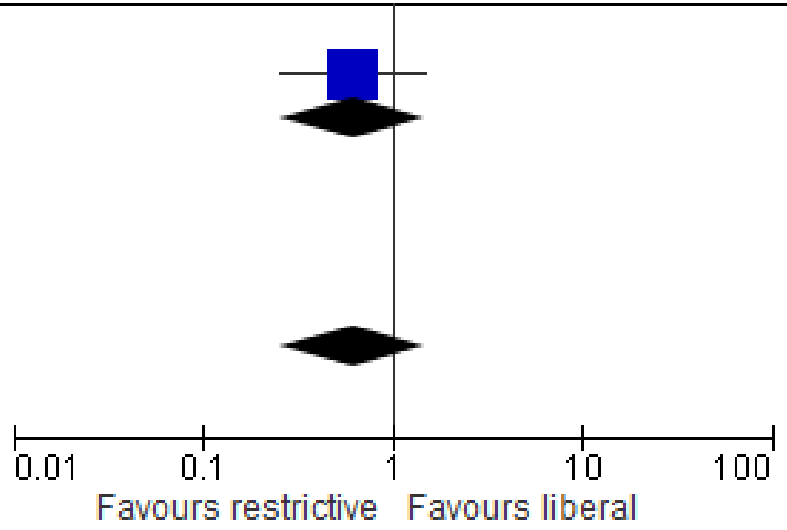


Acute intervention & intensive care

Acute (gastrointestinal) bleeding

CRITICAL OUTCOME: myocardial infarction

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Acute gastrointestinal bleeding						
Villanueva 2013	8	444	13	445	100.0%	0.62 [0.26, 1.47]
Subtotal (95% CI)		**444**		**445**	**100.0%**	**0.62 [0.26, 1.47]**
Total events	8		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						
Total (95% CI)		**444**		**445**	**100.0%**	**0.62 [0.26, 1.47]**
Total events	8		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						
Test for subgroup differences: Not applicable						

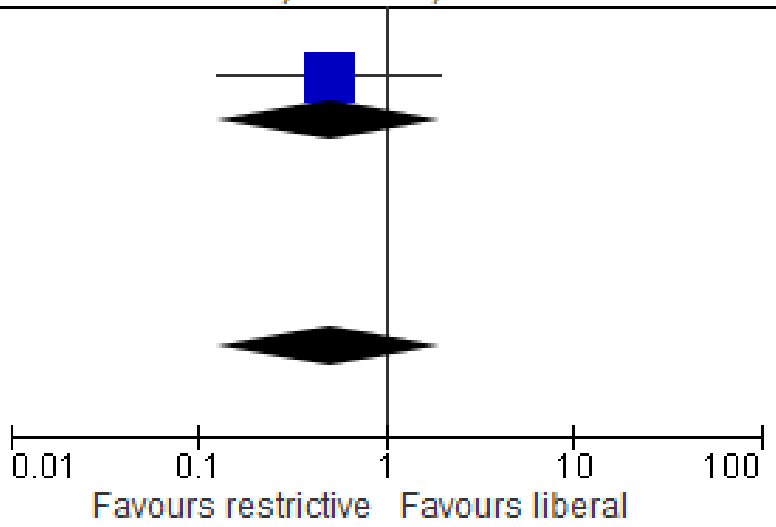


Acute intervention & intensive care

Acute (gastrointestinal) bleeding

CRITICAL OUTCOME: CVA-stroke

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Acute gastrointestinal bleeding						
Villanueva 2013	3	444	6	445	100.0%	0.50 [0.13, 1.99]
Subtotal (95% CI)		**444**		**445**	**100.0%**	**0.50 [0.13, 1.99]**
Total events	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
Total (95% CI)		**444**		**445**	**100.0%**	**0.50 [0.13, 1.99]**
Total events	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
Test for subgroup differences: Not applicable						

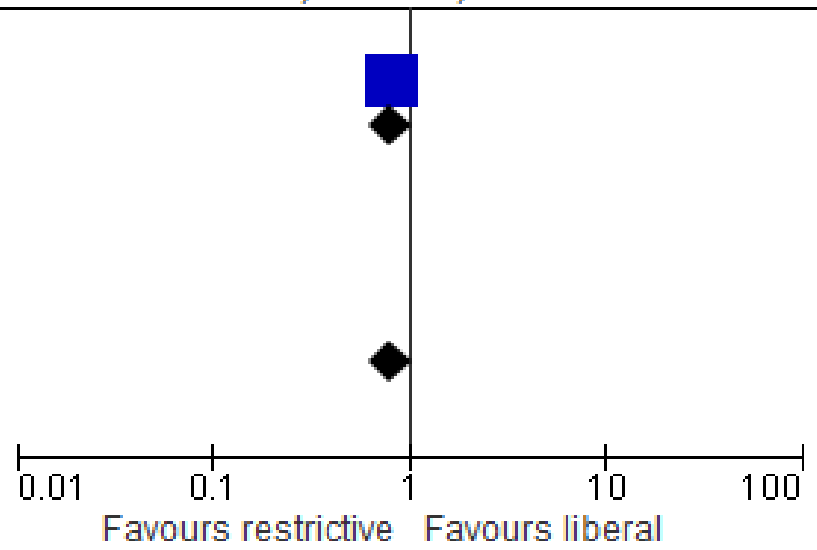


Acute intervention & intensive care

Acute (gastrointestinal) bleeding

CRITICAL OUTCOME: renal failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Acute gastrointestinal bleeding						
Villanueva 2013	78	444	97	445	100.0%	0.81 [0.62, 1.05]
Subtotal (95% CI)		**444**		**445**	**100.0%**	**0.81 [0.62, 1.05]**
Total events	78		97			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
Total (95% CI)		**444**		**445**	**100.0%**	**0.81 [0.62, 1.05]**
Total events	78		97			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Not applicable						



Acute intervention & intensive care

Acute gastrointestinal bleeding

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (<7-8 g/dL) versus liberal (<9-10 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Patients exposed to RBC transfusion	**296 fewer per 1.000** (388 fewer to 164 fewer)	**RR 0.55** (0.41 to 0.75)
RBC units transfused	MD **1.79 units lower** (3 lower to 0.58 lower)	-
Haemoglobin concentration	MD **0.89 lower** (1.01 lower to 0.77 lower)	-
Congestive heart failure	**20 fewer per 1.000** (34 fewer to 7 more)	**RR 0.57** (0.29 to 1.15)
Rebleeding	**56 fewer per 1.000** (84 fewer to 121 more)	**RR 0.54** (0.31 to 1.99)
Pneumonia	**11 fewer per 1.000** (42 fewer to 36 more)	**RR 0.90** (0.61 to 1.33)
Pneumonia or wound infection	**11 fewer per 1.000** (58 fewer to 47 more)	**RR 0.96** (0.79 to 1.17)
Function and fatigue (EQ-5D)	MD **0.07 points higher** (0 to 0.14 higher)	-

Undesirable effects?

NONE

Acute intervention & intensive care

Acute bleeding

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (70-80% of RBC volume) versus liberal (100% of RBC volume))	Relative effect (95% CI)
Blood usage (units)	MD **6.5 units lower** (12.21 lower to 0.79 lower)	-
Number of participants transfused	**320 fewer per 1.000** (550 fewer to 40 more)	**RR 0.68** (0.45 to 1.04)

Undesirable effects?

NONE

Acute intervention & intensive care

Quality of the body of evidence (critical outcomes)?

Acute gastrointestinal bleeding

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕⊕◯◯ LOW[a,b]
Hospital mortality	⊕◯◯◯ VERY LOW[a,b,c]
Myocardial infarction	⊕⊕◯◯ LOW[b,d]
CVA-stroke	⊕⊕◯◯ LOW[b,d]
Renal failure	⊕⊕◯◯ LOW[b,d]
30-day mortality (subgroup: patients with cirrhosis)	⊕⊕◯◯ LOW[b]

a. Risk of bias: selection bias, performance bias and detection bias
b. Imprecision: Limited sample size, low number of events and/or large variability of the results
c. Indirectness: study from the 1980s, not generalizible to the 2018 context
d. Risk of bias: detection bias (outcome assessors were not blinded)

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2018

Haematology & Oncology

Haematological patients
Patients with solid tumours

Richard Gammon

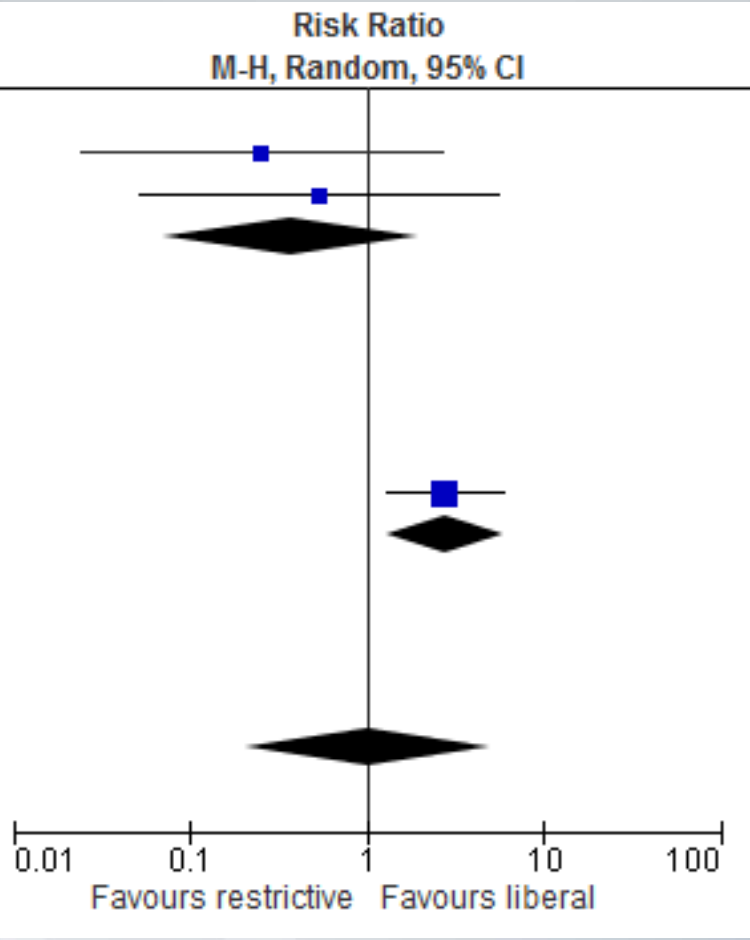
study characteristics

Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Haematology				
DeZern, 2016, USA	RCT	89 acute leukaemia participants (acute myeloid leukaemia, acute lymphoblastic leukaemia/lymphoma, acute promyelocytic leukaemia, treatment-related myeloid neoplasm, highgrade myelodysplastic syndrome)	Single-unit RBC transfusion if Hb <7 g/dL	Single-unit RBC transfusion if Hb <8 g/dL
Webert, 2008, Canada	RCT	60 adult participants with acute leukaemia	2- unit RBC transfusion if Hb <8 g/dL, with a target range of 8.5 to 9.5 g/dL	2-unit RBC transfusion if Hb <12 g/dL
Oncology				
De Almeida, 2015, Brazil	RCT	198 adult participants who underwent a major surgical procedure for abdominal cancer and required postoperative care in the ICU	RBC transfusion if Hb <7 g/dL	RBC transfusion if Hb <9 g/dL
Park, 2008, South Korea	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	RBC transfusion if Hb <10 g/dL	RBC transfusion if Hb <12 g/dL
Yakymenko, 2017, Denmark	RCT	133 patients with a confirmed diagnosis of malignant solid tumour and planned treatment with chemotherapy	RBC transfusion if Hb <9.7 g/dL	RBC transfusion if Hb <11.5 g/dL (females) or <13.1 g/dL (males)

Haematology & Oncology

CRITICAL OUTCOME: 30-day mortality

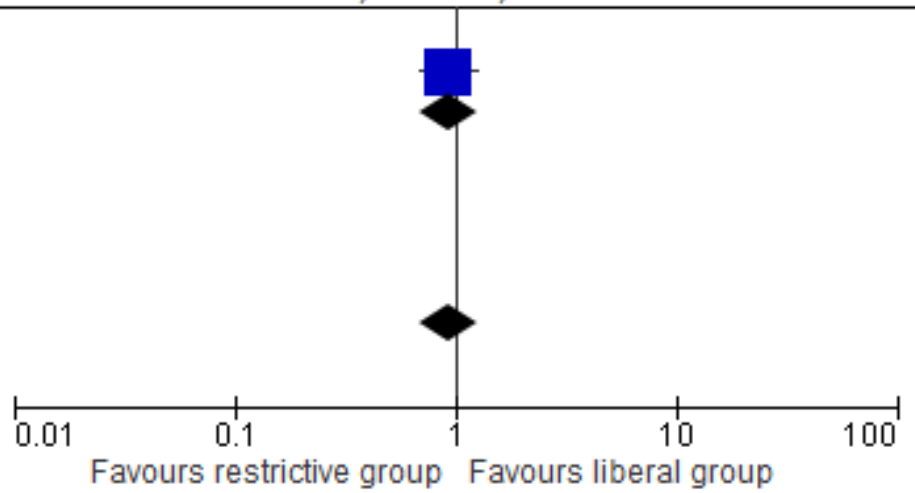
Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Haematology						
DeZern 2016	1	59	2	30	25.1%	0.25 [0.02, 2.69]
Webert 2008	1	29	2	31	25.2%	0.53 [0.05, 5.58]
Subtotal (95% CI)		**88**		**61**	**50.3%**	**0.37 [0.07, 1.95]**
Total events	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
1.1.2 Oncology						
De Almeida 2015	23	101	8	97	49.7%	2.76 [1.30, 5.87]
Subtotal (95% CI)		**101**		**97**	**49.7%**	**2.76 [1.30, 5.87]**
Total events	23		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.64 (P = 0.008)						
Total (95% CI)		**189**		**158**	**100.0%**	**1.00 [0.20, 4.93]**
Total events	25		12			
Heterogeneity: Tau² = 1.18; Chi² = 4.85, df = 2 (P = 0.09); I² = 59%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 4.66, df = 1 (P = 0.03), I² = 78.5%						



Oncology

CRITICAL OUTCOME: renal failure

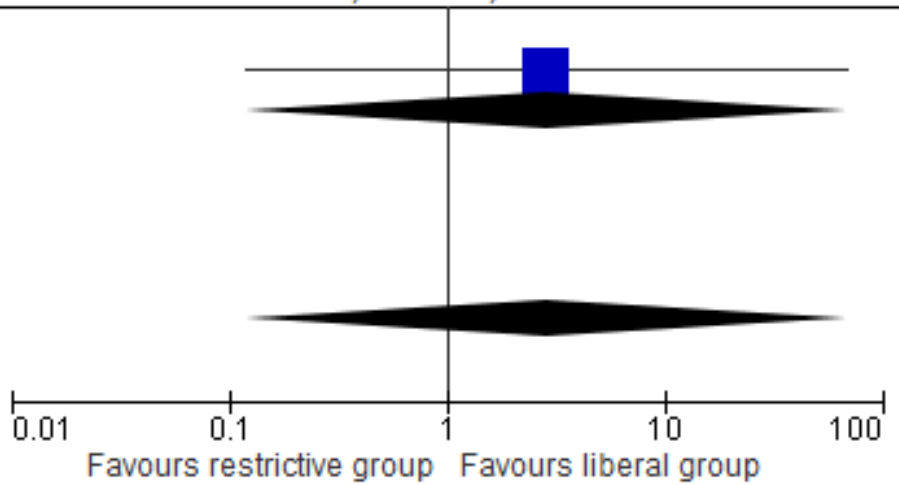
Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Oncology						
de Almeida 2015	44	101	45	97	100.0%	0.94 [0.69, 1.28]
Subtotal (95% CI)		**101**		**97**	**100.0%**	**0.94 [0.69, 1.28]**
Total events	44		45			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
Total (95% CI)		**101**		**97**	**100.0%**	**0.94 [0.69, 1.28]**
Total events	44		45			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Not applicable						



Oncology

CRITICAL OUTCOME: myocardial infarction

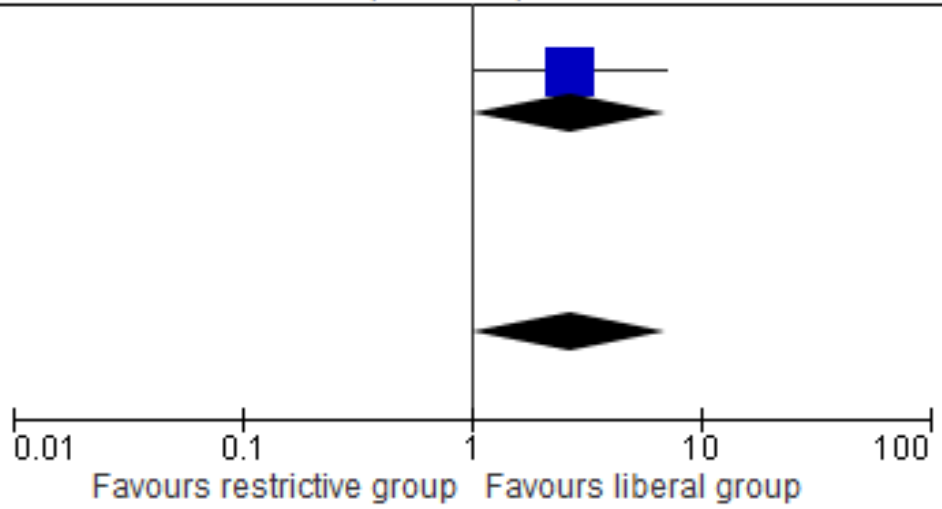
Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Oncology						
de Almeida 2015	1	101	0	97	100.0%	2.88 [0.12, 69.91]
Subtotal (95% CI)		**101**		**97**	**100.0%**	**2.88 [0.12, 69.91]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**101**		**97**	**100.0%**	**2.88 [0.12, 69.91]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Test for subgroup differences: Not applicable						



Oncology

CRITICAL OUTCOME: cardiac events

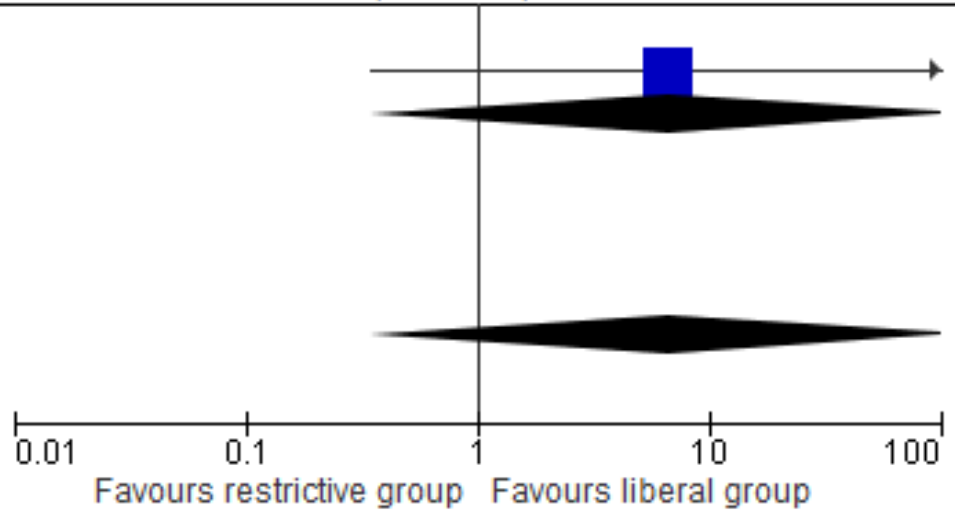
Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Oncology						
de Almeida 2015	14	101	5	97	100.0%	2.69 [1.01, 7.18]
Subtotal (95% CI)		**101**		**97**	**100.0%**	**2.69 [1.01, 7.18]**
Total events	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**101**		**97**	**100.0%**	**2.69 [1.01, 7.18]**
Total events	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Not applicable						



Oncology

CRITICAL OUTCOME: CVA-stroke

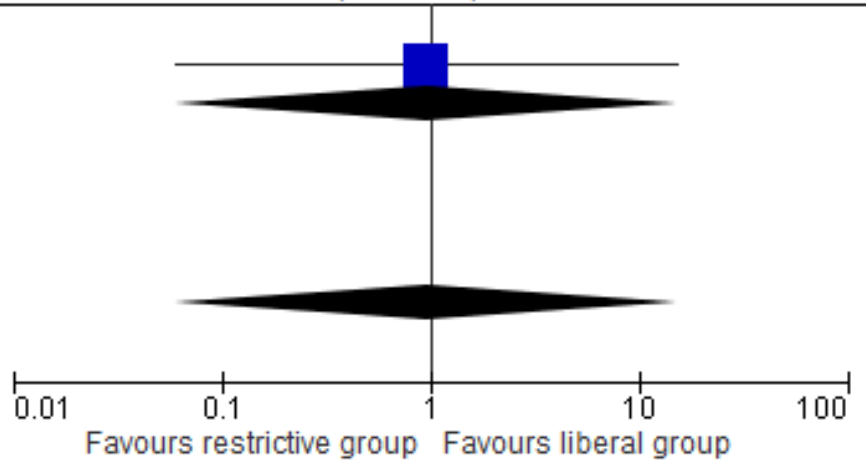
Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 Oncology						
de Almeida 2015	3	101	0	97	100.0%	6.73 [0.35, 128.52]
Subtotal (95% CI)		**101**		**97**	**100.0%**	**6.73 [0.35, 128.52]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.21)						
Total (95% CI)		**101**		**97**	**100.0%**	**6.73 [0.35, 128.52]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.21)						
Test for subgroup differences: Not applicable						



Oncology

CRITICAL OUTCOME: thromboembolism

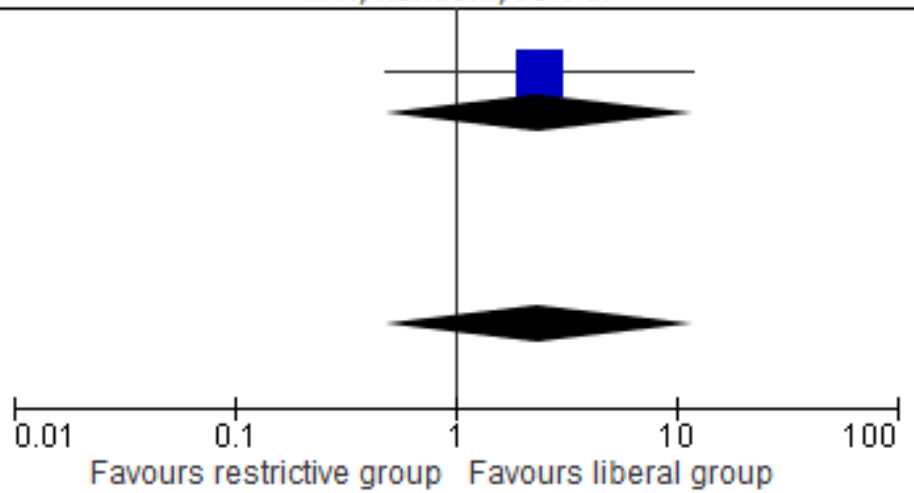
Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.24.1 Oncology						
de Almeida 2015	1	101	1	97	100.0%	0.96 [0.06, 15.14]
Subtotal (95% CI)		**101**		**97**	**100.0%**	**0.96 [0.06, 15.14]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Total (95% CI)		**101**		**97**	**100.0%**	**0.96 [0.06, 15.14]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Not applicable						



Oncology

CRITICAL OUTCOME: congestive heart failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Oncology						
de Almeida 2015	5	101	2	97	100.0%	2.40 [0.48, 12.08]
Subtotal (95% CI)		**101**		**97**	**100.0%**	**2.40 [0.48, 12.08]**
Total events	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**101**		**97**	**100.0%**	**2.40 [0.48, 12.08]**
Total events	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						



Haematology & oncology

Haematology

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (<7/8 g/dL) versus liberal (<8/12 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
RBC transfusion (units)	MD **3.1 RBC units lower** (5.31 lower to 0.89 lower)	-
Patients received RBC transfusion	**0 fewer per 1.000** (48 fewer to 48 more)	**RR 1.00** (0.95 to 1.05)
Episodes of neutropenic fever (0-1 vs 2-5)	**88 fewer per 1.000** (249 fewer to 125 more)	**RR 0.88** (0.66 to 1.17)
Length of inpatient stay (days)	median **0.5 days lower** (0 to 0)	-
Fatigue scale score	median **0.3 points higher** (0 to 0)	-

Undesirable effects?

Outcomes	Difference (restrictive (<7/8 g/dL) versus liberal (<8/12 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Bleeding events (by grade: 0-1 vs 2-4)	**17 more per 1.000** (133 fewer to 192 more)	**RR 1.02** (0.84 to 1.23)

Haematology & oncology

Oncology

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (<7/9.7/10 g/dL) versus liberal (<9/11.5/12 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Patients exposed to RBC transfusions	**160 fewer per 1.000** (252 fewer to 24 fewer)	**RR 0.67** (0.48 to 0.95)
Transfusion-related fever	**51 fewer per 1.000** (153 fewer to 184 more)	**RR 0.78** (0.34 to 1.79)

Undesirable effects?

Outcomes	Difference (<7/9.7/10 g/dL) versus liberal (<9/11.5/12 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Sepsis-bacteraemia	**7 more per 1.000** (43 fewer to 138 more)	**RR 1.10** (0.41 to 2.91)
Pneumonia	**84 more per 1.000** (17 fewer to 273 more)	**RR 1.63** (0.87 to 3.04)
Pneumonia or wound infection	**91 more per 1.000** (26 fewer to 279 more)	**RR 1.42** (0.88 to 2.29)
Thromboembolism	**0 fewer per 1.000** (10 fewer to 149 more)	**RR 0.96** (0.06 to 15.47)

Haematology & Oncology

Quality of the body of evidence (critical outcomes)?

Haematology

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕⊕◯◯ LOW[a,b]

a. Limited sample size or low number of events
b. Large variability of results

Oncology

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕◯◯◯ VERY LOW[a,b]
Renal failure	⊕◯◯◯ VERY LOW[a,b]
Myocardial infarction	⊕◯◯◯ VERY LOW[a,b]
Cardiac events	⊕⊕◯◯ LOW[a,b]
CVA-stroke	⊕◯◯◯ VERY LOW[a,b]
Thromboembolism	⊕◯◯◯ VERY LOW[a,b]

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

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2018

Neurology

Patients with acute central nervous injury
Patients with cerebral perfusion disorders

Cynthia So-Osman

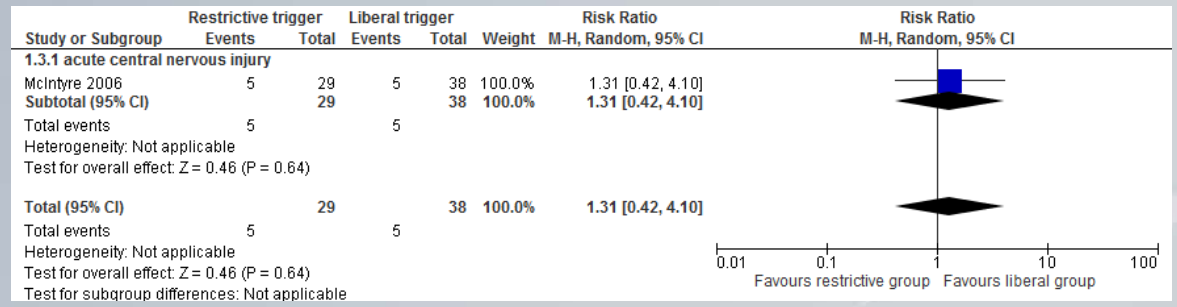
study characteristics

Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Patients with acute central nervous injury				
McIntyre, 2006, Canada	RCT	67 multiple trauma patients with a closed head injury	Single-unit RBC transfusion if Hb <7 g/dL	Single-unit RBC transfusion if Hb <10 g/dL
Ngwenya, 2017, USA	Cohort study	1565 consecutive patients with a diagnosis of traumatic brain injury	Hb <7 g/dL	Hb <10 g/dL
Patients with cerebral perfusion disorders				
Naidech, 2010, USA	RCT	44 patients with subarachnoid hemorrhage and high risk for vasospasm	Hb <10 g/dL	Hb <11.5 g/dL

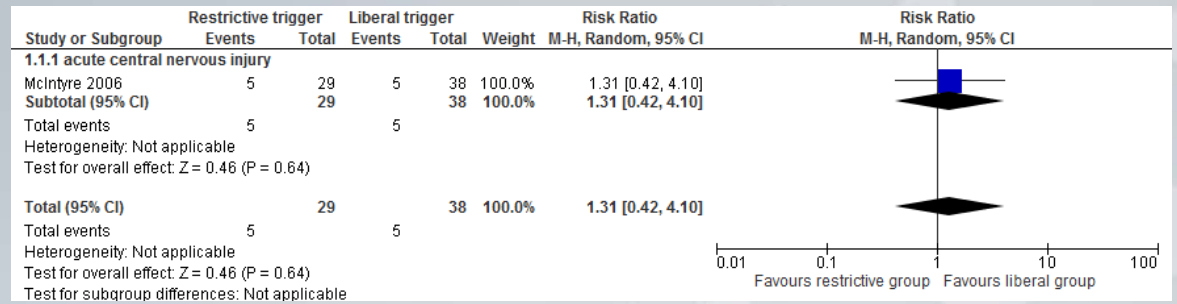
Acute central nervous injury

CRITICAL OUTCOME: hospital/30-day/60-day mortality

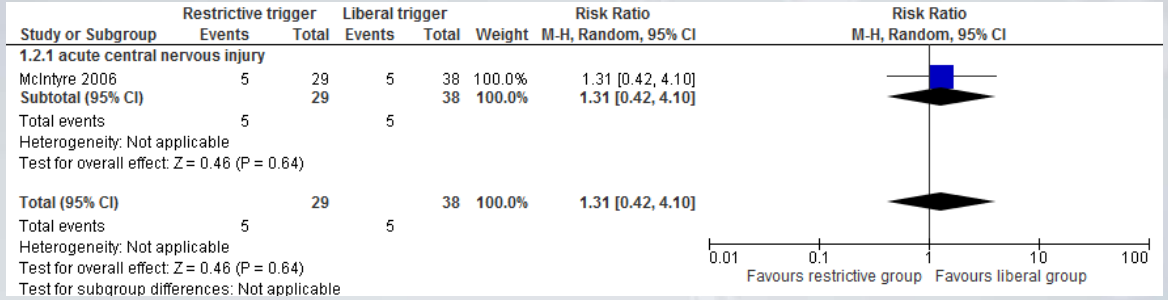
Hospital mortality



30-day mortality



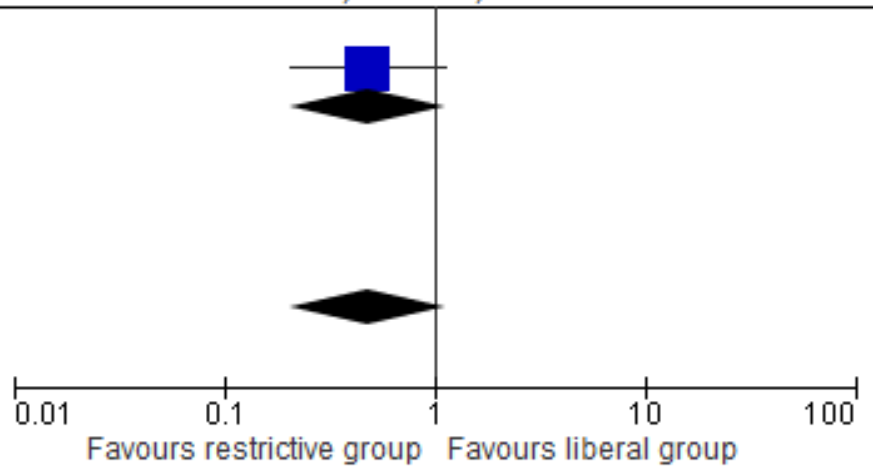
60-day mortality



Acute central nervous injury

CRITICAL OUTCOME: ARDS/ALI

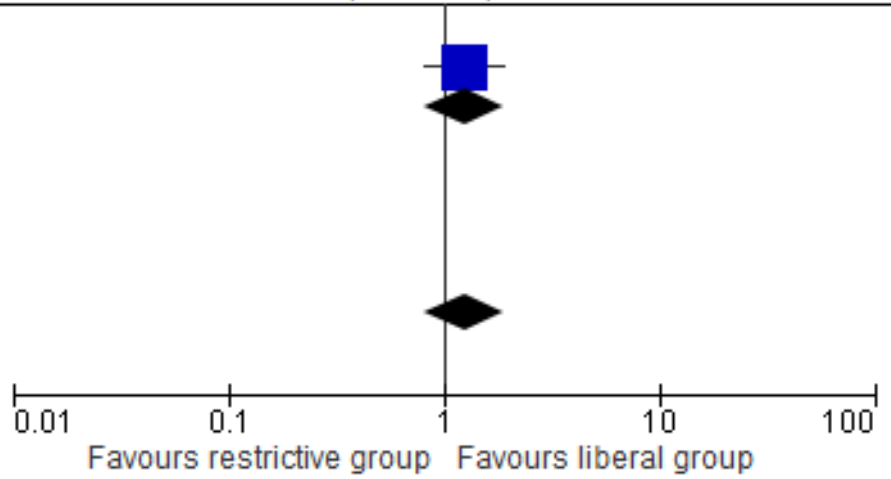
Study or Subgroup	Restrictive trigger Events	Total	Liberal trigger Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 acute central nervous injury						
Ngwenya 2017	7	561	22	848	100.0%	0.48 [0.21, 1.12]
Subtotal (95% CI)		**561**		**848**	**100.0%**	**0.48 [0.21, 1.12]**
Total events	7		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
Total (95% CI)		**561**		**848**	**100.0%**	**0.48 [0.21, 1.12]**
Total events	7		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: Not applicable						



Acute central nervous injury

CRITICAL OUTCOME: thromboembolism

Study or Subgroup	Restrictive trigger Events	Total	Liberal trigger Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 acute central nervous injury						
Ngwenya 2017	38	561	46	848	100.0%	1.25 [0.82, 1.89]
Subtotal (95% CI)		**561**		**848**	**100.0%**	**1.25 [0.82, 1.89]**
Total events	38		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
Total (95% CI)		**561**		**848**	**100.0%**	**1.25 [0.82, 1.89]**
Total events	38		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
Test for subgroup differences: Not applicable						



Acute central nervous injury

CRITICAL OUTCOMES: hospital mortality/ARDS-ALI/thromboembolism (subgroup analyses: patients with GCS score ≤8)

Outcomes	Difference (restrictive (<7 g/dL) versus liberal (<10 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Hospital mortality (patients with GCS ≤8)	**98 fewer per 1.000** (171 fewer to 13 more)	**RR 0.69** (0.46 to 1.04)
ARDS/ALI in patients with GCS ≤8	**39 fewer per 1.000** (68 fewer to 36 more)	**RR 0.54** (0.20 to 1.43)
DVT/PE in patients with GCS ≤8	**16 more per 1.000** (42 fewer to 130 more)	**RR 1.16** (0.59 to 2.28)

Neurology

Acute central nervous injury

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (<7 g/dL) versus liberal (<10 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Days requiring mechanical ventilation	MD **0.8 days fewer** (3.19 fewer to 1.59 more)	-
Number of RBC transfusions (units per patient)	MD **3.2 units per patient lower** (4.33 lower to 2.07 lower)	-
Proportion transfused	**410 fewer per 1.000** (560 fewer to 200 fewer)	**RR 0.59** (0.44 to 0.80)

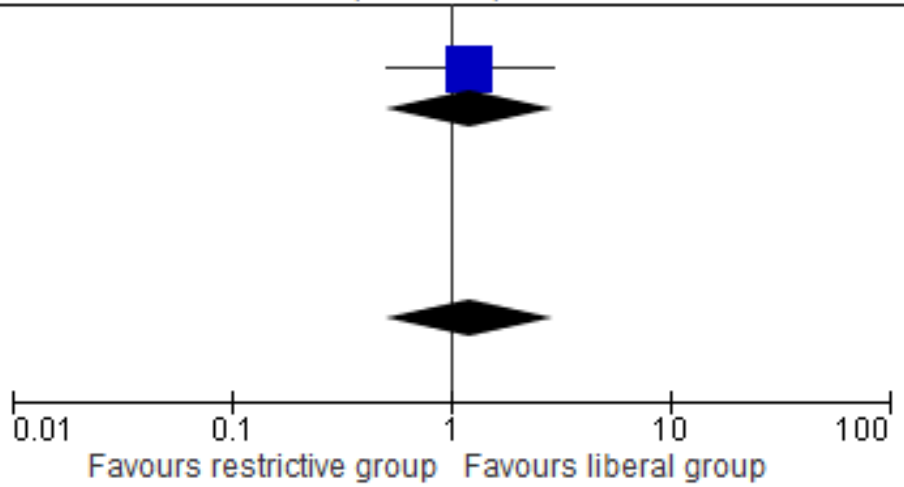
Undesirable effects?

Outcomes	Difference (restrictive (<7 g/dL) versus liberal (<10 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
ICU length of stay	MD **1.2 days more** (2.13 more to 4.53 more)	-
Multiple organ dysfunction	MD **0.7 higher** (1.07 lower to 2.47 higher)	-
Proportion who developed infection	**16 more per 1.000** (42 fewer to 408 more)	**RR 1.31** (0.20 to 8.76)

Cerebral perfusion disorders

CRITICAL OUTCOME: any adverse event related to transfusion

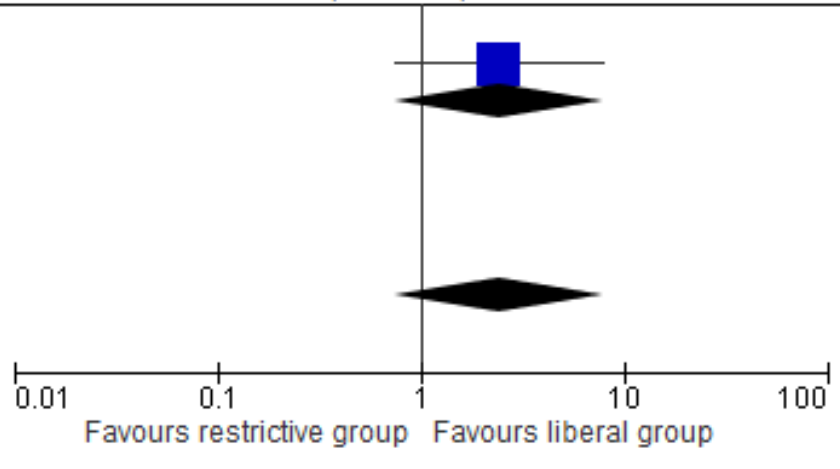
Study or Subgroup	Restrictive group Events	Total	Liberal group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Cerebral perfusion disorders						
Naidech 2010	8	23	6	21	100.0%	1.22 [0.51, 2.93]
Subtotal (95% CI)		**23**		**21**	**100.0%**	**1.22 [0.51, 2.93]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**23**		**21**	**100.0%**	**1.22 [0.51, 2.93]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Not applicable						



Cerebral perfusion disorders

CRITICAL OUTCOME: pulmonary edema or respiratory distress

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Cerebral perfusion disorders						
Naidech 2010	8	23	3	21	100.0%	2.43 [0.74, 7.99]
Subtotal (95% CI)		**23**		**21**	**100.0%**	**2.43 [0.74, 7.99]**
Total events	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**23**		**21**	**100.0%**	**2.43 [0.74, 7.99]**
Total events	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Not applicable						



Neurology

Cerebral perfusion disorders

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (<10 g/dL) versus liberal (<11.5 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Any packed RBC transfusion given	**124 fewer per 1.000** (286 fewer to 67 more)	**RR 0.87** (0.70 to 1.07)
Total packed RBC units given per patient	median **1 units per patient fewer**	-

Undesirable effects?

Outcomes	Difference (restrictive (<10 g/dL) versus liberal (<11.5 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Ventilar-free days	median **2 days more**	-
Any cerebral infarction on MRI	**108 more per 1.000** (123 fewer to 645 more)	**RR 1.36** (0.59 to 3.15)
Delayed cerebral infarction	**51 more per 1.000** (180 fewer to 489 more)	**RR 1.12** (0.58 to 2.14)

Neurology

Quality of the body of evidence (critical outcomes)?

Acute central nervous injury

Outcomes	Certainty of the evidence (GRADE)
Hospital mortality	⊕◯◯◯ VERY LOW[a,b]
Hospital mortality (patients with GCS ≤8)	⊕◯◯◯ VERY LOW[a,b]
ARDS/ALI	⊕◯◯◯ VERY LOW[a,b]
ARDS/ALI in patients with GCS ≤8	⊕◯◯◯ VERY LOW[a,b]
DVT/PE	⊕◯◯◯ VERY LOW[a,b]
DVT/PE in patients with GCS ≤8	⊕◯◯◯ VERY LOW[a,b]
30-day/60-day/hospital mortality	⊕◯◯◯ VERY LOW[b,c]

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

Cerebral perfusion disorders

Outcomes	Certainty of the evidence (GRADE)
Any adverse event related to transfusion	⊕◯◯◯ VERY LOW[a,b]
Pulmonary edema or respiratory distress	⊕◯◯◯ VERY LOW[a,b]

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