

Appendix 1:

Search strategies for

Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion

Updated searches from 2011 to October 1st 2014

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 8 of 12, 2014) in *The Cochrane Library* (148 hits in CENTRAL)

#1 MeSH descriptor: [Blood Transfusion] explode all trees and with qualifiers: [Methods - MT, Standards - ST]

#2 transfus* near/5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard* or requir*)

#3 (red blood cell* or RBC) near/5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*) and (therap* or transfus*)

#4 (h?emoglobin or h?emocrit or HB or HCT) near/5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)

#5 transfus* near/5 (restrict* or liberal*)

#6 (blood transfus*) near/3 (management or program*)

#7 (#1 or #2 or #3 or #4 or #5 or #6) from 2011 to 2014

MEDLINE (Ovid SP)(2011 to September 2014)(605 hits)

1. exp Blood Transfusion/

2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

3. 1 or 2

4. exp Reference Standards/

5. standards.fs.

6. methods.fs.

7. 4 or 5 or 6

8. 3 and 7

9. (transfus* adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard* or requir*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

10. ((red blood cell* or RBC) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

11. ((h?emoglobin or h?emocrit or HB or HCT) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp. [mp=protocol supplementary concept, rare disease

supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

12. (transfus* adj5 (restrict* or liberal*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

13. ((blood or transfus*) adj3 (management or program*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

14. 8 or 9 or 10 or 11 or 12 or 13

15. randomized controlled trial.pt.

16. controlled clinical trial.pt.

17. clinical trials as topic.sh.

18. random*.ab,ti.

19. trial.ti.

20. placebo.ab.

21. 15 or 16 or 17 or 18 or 19 or 20

22. (animals not (humans and animals)).sh.

23. 21 not 22

24. 14 and 23

25. limit 24 to yr="2011 -Current"

EMBASE (Ovid SP)(2011 to September 2014)(1075 hits)

1. exp blood transfusion/

2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

3. 1 or 2

4. exp STANDARD/

5. 3 and 4

6. (transfus* adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard* or requir*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

7. ((red blood cell* or RBC) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

8. ((h?emoglobin or h?emocrit or HB or HCT) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

9. (transfus* adj5 (restrict* or liberal*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
10. ((blood or transfus*) adj3 (management or program*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp controlled clinical trial/
13. random*.ab,ti.
14. trial.ti.
15. placebo.ab.
16. 12 or 13 or 14 or 15
17. exp animal/ not (exp human/ and exp animal/)
18. 16 not 17
19. 11 and 18
20. limit 19 to yr="2011 -Current"

Science Citation Index Expanded (SCI-EXPANDED)(2011 to Septembers 2014)(155 hits)

#7 121 #6 AND #1

#6 22,416 #5 AND #4

#5 282,080 TS=(human*)

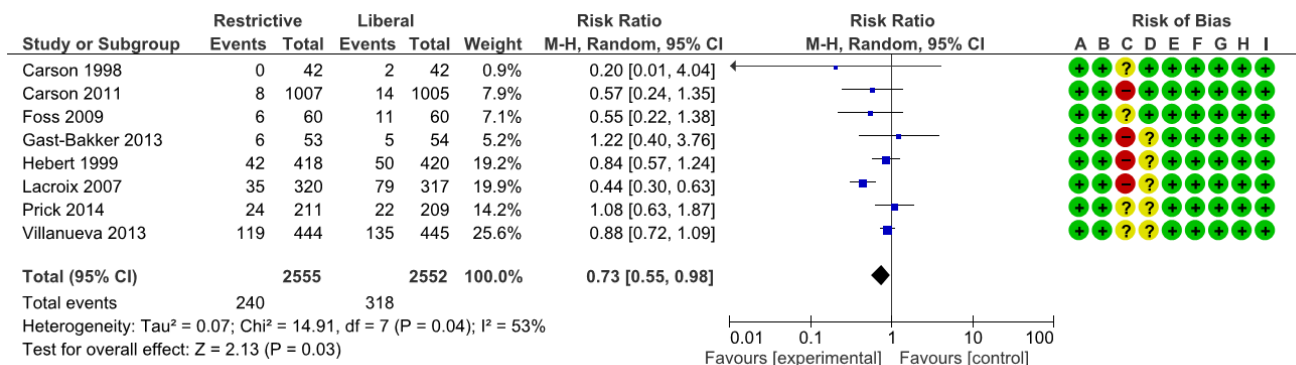
#4 216,088 #3 OR #2

#3 26,919 TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))

#2 210,011 TS=(random* OR ((controlled OR clinical) AND trial) OR placebo)

#1 3,259 TS=((blood OR (red blood cell*) OR RBC OR hemoglobin* OR haemoglobin* OR haemocrit OR hemocrit OR HB OR HCT) AND transfus* AND (polic* OR practice OR protocol* OR trigger* OR threshold* OR indicator* OR strateg* OR criteri* OR standard* OR restrict* OR liberal* OR management OR program*))

Appendix 2 : Forest plot of number of infectious complications in lower risk of bias trials. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represents 95% confidence intervals

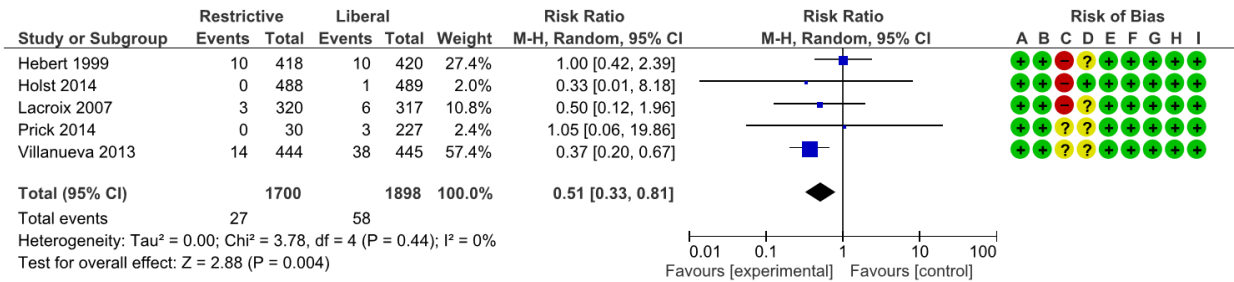


Risk of bias legend

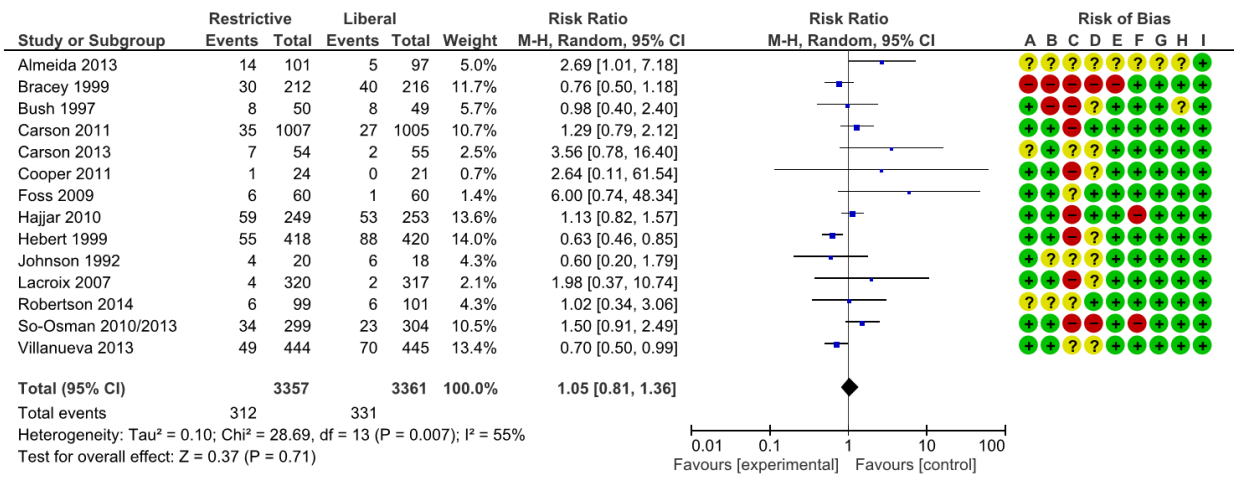
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Baseline Imbalance
- (H) Sponsor bias
- (I) Academic bias

Appendix 2: Other adverse events, all trials

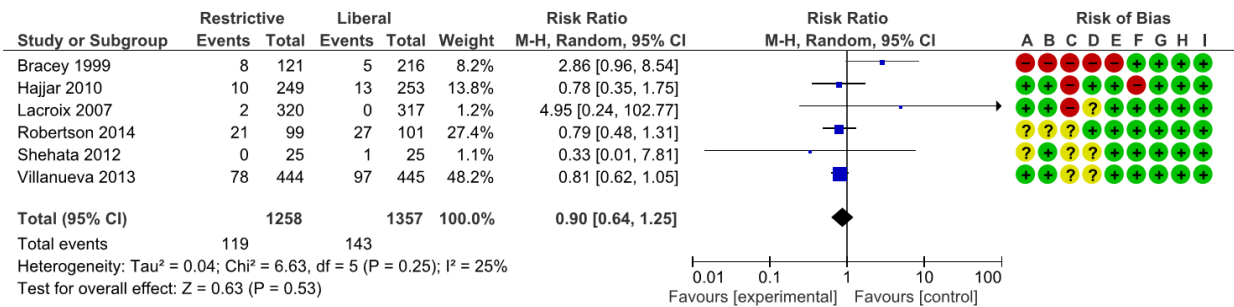
Transfusion reactions



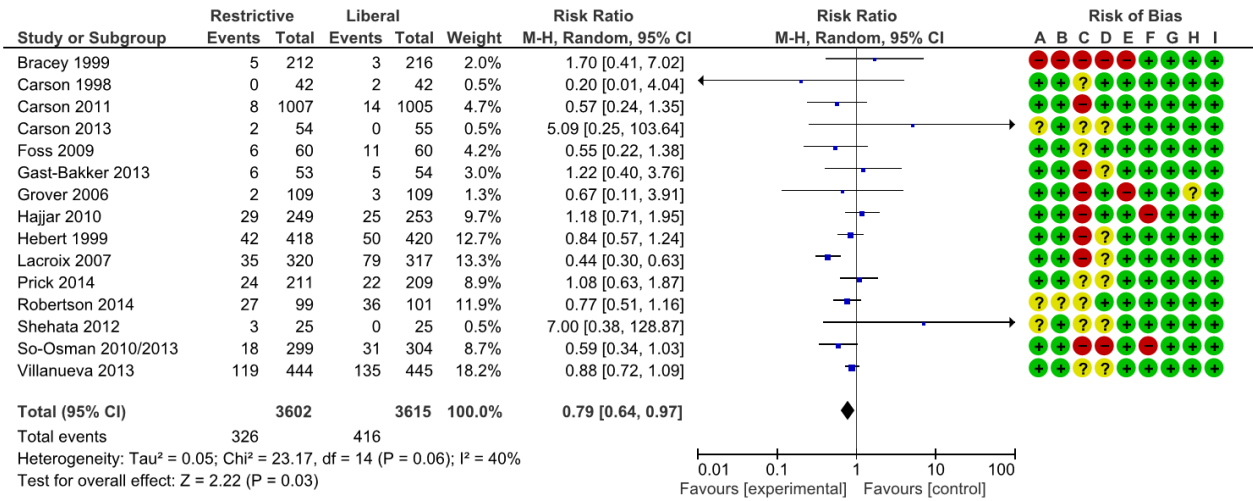
Cardiac complications (not including fatal and non-fatal myocardial infarction)



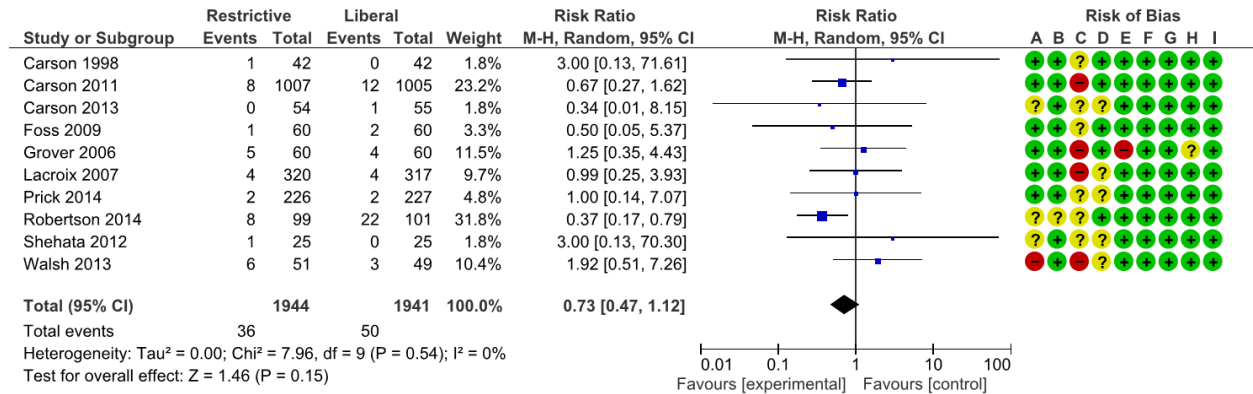
Renal failure



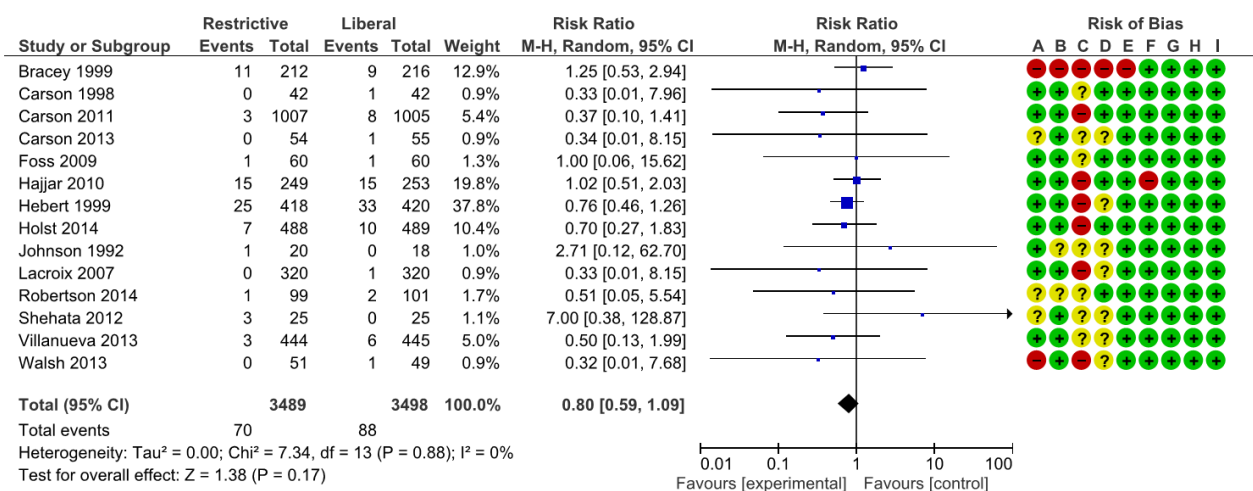
Infectious Complications



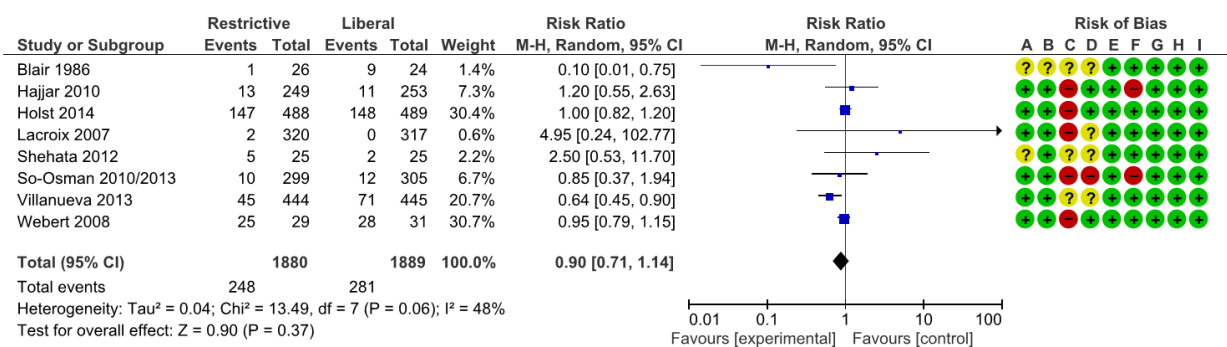
Thromboembolic events



Stroke or Transitory cerebral ischemia



Haemorrhagic events



Trial ID*	Mortality	Morbidity Overall	Transfusion reactions	Myocardial infarction	Cardiac complications	Renal failure	Infectious complications	Thromboembolic complications	Stroke/TCI	Haemorrhagic events	Other adverse outcomes
Almeida 2013	60 day, R: 23/101, L: 8/97	NA	NA	NA	Cardiac complications, R: 14/101, L: 5/97	NA	NA	NA	NA	NA	NA
Blair 1986	Unspecified follow up, R: 0/26, L: 2/24	NA	NA	NA	NA	NA	NA	NA	NA	Re-bleeding, R:1/26, L: 9/24	NA
Bracey 1999	During hospitalization for surgery (reported for included and excluded patients), R: 3/215, L: 6/222	NA	NA	MI, R: 1/212, L: 0/216	Atrial arrhythmia, R: 30/212, L: 40/216; Ventricular arrhythmia, R: 13/212, L: 9/216	Renal failure, R: 8/212, L: 5/216	Infection, R: 5/212, L: 3/216	NA	Neurologic event [§] , R: 11/212, L: 9/216	NA	Pulmonary complications ^{§§} , R: 57/212, L: 64/216
Bush 1997	30 day, R: 4/50, L: 4/49	NA	NA	Intraoperative MI, R: 1/50, L: 3/49	Q waves on ECG, arrhythmia or MI, R: 8/50, L: 8/49	NA	NA	NA	NA	NA	NA
Carson 1998	60 day, R: 5/42, L: 2/42	NA	NA	MI, R: 0/42, L: 0/42	NA	NA	Pneumonia, R: 0/42, L: 2/42	Thromboembolism, R: 1/42, L: 0/42	Stroke, R: 0/42, L: 1/42	NA	Death or inability to walk 10 ft. without assistance, R:

											16/42, L:19/42
Carson 2011	60 day all cause, R: 66/1001, L: 76/998	Death and inability to walk 10 ft. independently at day 60, R: 347/1001, L: 351/998	NA	MI, R: 38/1008, L: 23/1005	Congestive heart disease, R: 35/1007, L: 27/1005	NA	Wound infection, R: 8/1007, L: 14/1005	DVT or pulmonary embolism, R: 8/1007, L: 12/1005	Stroke or TCI diagnosed by physician, CT or MRI, R: 3/1007, L: 8/1005	NA	
Carson 2013	30 day, R: 7/54, L: 1/55	Death/MI/unscheduled revascularisation/unscheduled cardiac admission, R: 17/54, L: 9/55	NA	MI, R: 7/54, L: 5/55	Congestive heart failure R: 7/54, L: 2/55 Unscheduled coronary revascularisation, R: 2/54, L: 0/55	NA	Pneumonia R: 2/54, L: 0/55	Thromboembolic events, R: 0/54, L: 1/55	Stroke, R: 0/54, L: 1/55	NA	Unscheduled hospital admission, R:17/54, L: 9/55;
Cooper 2011	30 day, R: 2/24, L: 1/21	Death/recurrent MI, or new/worsening HF, or recurrent ischemia, R: 13/24,	NA	Recurrent in-hospital ischemia, R: 1/24, L: 0/21	NA	NA	NA	NA	NA	NA	In-hospital death, recurrent MI, or new or worsening HF at day 30, R: 5/24, L: 13/21

1987											
Foss 2009	30 day, R: 5/60, L: 0/60	NA	NA	MI, R: 1/60, L: 0/60	Any cardiovascular event, R: 6/60, L: 1/60; Acute arrhythmia, R: 3/60, L: 1/60;	NA	Any infectious complications, R: 6/60, L: 11/60; Sepsis, R: 1/60, L: 1/60	Thromboembolic event, R: 1/60, L: 2/60	Cerebrovascular event, R: 1/60, L: 1/60	NA	Pulmonary edema/congestive heart disease, R: 1/60, L: 1/60;
Grover 2005	3 day (?), R: 0/109, L: 1/109	NA	NA	Silent MI, R: 21/109, L: 26/109; MI, R: 0/109, L: 1/109;	LBBB [‡] , R: 2/109, L: 1/109; Ventricular tachycardia, R: 2/109, L: 0/109;	NA	Wound infection, R: 2/109, L: 3/109; Chest infection, R: 2/109, L: 3/109	DVT, R: 5/60, L: 4/60; Pulmonary embolism, R: 2/109, L: 1/109;	NA	NA	
Hajjar 2010	30 day, R: 15/249, L: 12/253	Any cardiac event ⁴ , R: 59/249, L: 53/253	NA	NA	Any cardiac event ^{##} , R: 59/249, L: 53/253; Cardiogenic shock, R: 22/249, L: 12/253	AKI requiring dialysis or haemofiltration, R: 10/249, L: 13/253	Infectious complications, R: 29/249, L: 25/253	NA	Neurologic complications, R: 15/249, L: 15/253	Bleeding, R: 13/249, L: 11/253	ARDS R: 5/249, L: 2/253

Hebert 1995	120 day, R: 13/33, L: 11/36; 30 day, R: 8/33, L: 9/36	Multiple organ failure (>3 organs), R: 9/33, L: 6/36	NA	NA	NA	NA	NA	NA	NA	NA	Hospital LOS, R: 38 (25-62)**, L: 31 (13-64); Mean organ dysfunction score, R: 9.3 (3.6), L: 10.0 (3.8)
Holst 2014	90 day all cause, R: 216/502, L: 223/496	NA	Acute haemolytic reaction, R: 0/488, L: 1/489	MI, R: 17/488, L: 6/489	NA	Days alive without RRT, R: 85, L: 83	NA	Limb: R:14/488, L: 11/489; Intestinal: R:14/488, L: 14/489	Cerebral ischemia: R: 7/488, L: 10/489	Haemorrhagic events, R: 147/488, L: 148/489	Days alive without vasopressors, R: 73, L: 75; Days alive without mechanical ventilation, R: 65, L: 67
Hebert 1999	60 day, R: 95/416, L:111/419	Any adverse event, R: 205/418, L: 228/420	Hematological complication [†] R: 10/418, L: 10/420	MI, R: 3/418, L: 12/420	Any cardiac complication [†] , R: 55/418, L: 88/420	NA	Infectious complication [†] , R: 42/418, L: 50/420	NA	Cerebrovascular accidents and encephalopathies, R: 25/418, L: 33/420	NA	Gastrointestinal complications ^{†††} R: 13/418, L: 19/420; Pulmonary complications R: 106/418, L: 50/420; Non-septic shock, R: 205/418, L: 228/420

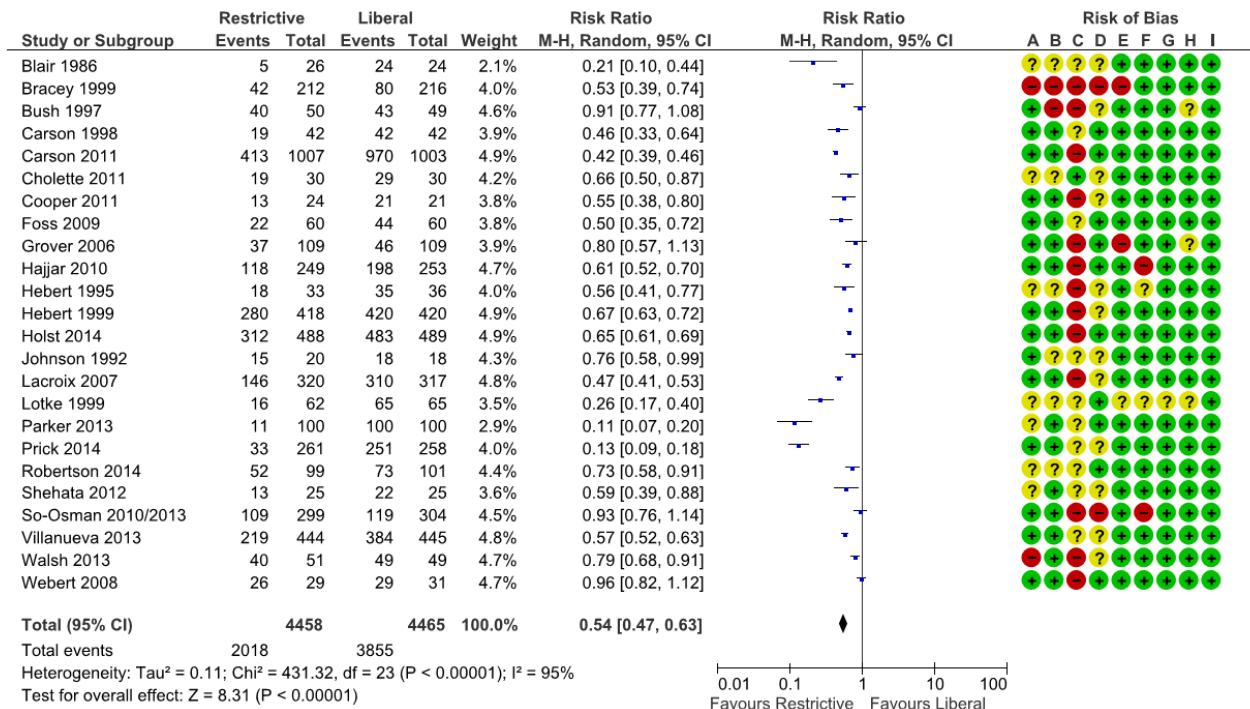
Johnson 1992	NA	NA	NA	Perioperative MI, R: 0/20, L: 1/18	Arrhythmias, R: 4/20, L: 6/18	NA	NA	NA	Cerebrovascular accident, R: 1/20, L: 0/18	NA	Pneumothorax, R: 2/20, L: 0/18; Pulmonary edema, R: 0/20, L: 1/18; Postpericardiotomy syndrome, R: 1/18, L: 1/20
Lacroix 2007	28 day, R: 14/320, L: 14/317	Adverse events, R: 97/329, L: 90/317	Reactions to RBC transfusion, R: 3/320, L: 6/317; Transfusion reactions, R: 2/320, L: 0/317	ST-elevation MI, R: 1/320, L: 0/317	Arrhythmia, R: 4/320, L: 2/317	Renal failure, R: 2/320, L: 0/317	Nosocomial infections, R: 65/320, L: 79/317; Sepsis, R: 3/320, L: 2/317	Thrombosis, R: 4/320 L: 4/317	Cerebral infarction, R: 0/320, L: 1/317	Cardiovascular bleeding, R: 2/320, L: 0/317; Lower GI-bleeding, R: 2/320, L: 0/317; Upper-GI bleeding, R: 2/320, L: 2/317	New or progressive MODS, R: 38/320, L: 39/317; No. of dysfunctional organs, R: 1.6 (1.4), L: 1.5 (1.2); Duration of mechanical ventilation, R: 6.2 (5.9), L: 6.0 (5.4); Fluid overload, R: 1/320, L: 3/317; DIC, R: 1/320, L: 0/317; Number of pts with one or more

											serious adverse events, R: 19/320, L: 19/317
Lotke 1999	NA	R: 16/62, L: 5/65	NA	MI, R: 1/62, L: 0/65	Dysarrhythmia, R: 1/62, L: 0/65	NA	NA	NA	NA	NA	Mental confusion, R: 7/62, L: 2/65; Lethargy, R: 4/62, L: 1/65; Orthostatic hypotension, R: 3/62, L: 2/65
Parker 2013	365 day, R: 26/100, L: 27/100; 30 day mortality, R: 5/100, L: 3/100; 90 mortality, R: 11/100, L: 10/100; 120 day mortality, R: 11/100, L: 13/100	NA	NA	NA	NA	NA	NA	NA	NA	NA	Total hospital LOS, R: 23.3, L: 21.8; Mean change in morbidity score, R: 2.0, L: 2.4
Prick 2012	NA	NA	R: 0/30, L: 3/227	NA	NA	NA	Total infectious complicati ons, R: 24/211, L: 22/209; Infected	Thromboe mbolic event, R: 2/226, L: 2/227	NA	NA	Endometritis, R: 3/225, L: 5/228

							surgery wound, R: 1/46, L: 0/41; Infected surgery spisiotomy, R: 6/145, L: 6/137				
Roberts on 2014	180 day, R: 14/99, L: 17/101	NA	NA	Acute MI, R: 1/99, L: 1/101	Cardiac arrest, R: 2/99, L: 2/101; Other cardiac complications, R: 6/99, L: 6/101	Acute renal failure, R: 21/99, L: 27/101	Infectious complications, R: 27/99, L: 36/101; Pneumonia, R: 13/99, L: 20/101; Sepsis R: 3/99, L: 5/101	Any tromboembolic event, R: 8/99, L: 22/101; Pulmonary embolus, R: 1/99, L: 6/101	Stroke, R: 1/99, L: 2/101	NA	ARDS, R: 16/99, L: 25/101
Shehata 2012	30 day all cause, R: 4/25, L: 1/25	Composite score , R: 14/25, L: 8/25	Transfusion reactions, R: 0/25, L: 0/25 ^a	Post operative MI, R: 1/25, L: 0/25	NA	Dialysis, R: 0/25, L: 1/25; >50% increase in S-	Sepsis, R: 3/25, L: 0/25; Pneumonia, R: 4/25, L: 0/25	Pulmonary embolus/DVT, R: 1/25, L: 0/25	Stroke, R: 3/25, L: 0/25	Haemorrhage, R: 1/25, L: 2/25	Use of inotropes >24 hours, R: 4/25, L: 2/25; MOF, R: 1/25, L: 0/25; Reintubation, R: 4/25, L: 1/25; Intubation >48

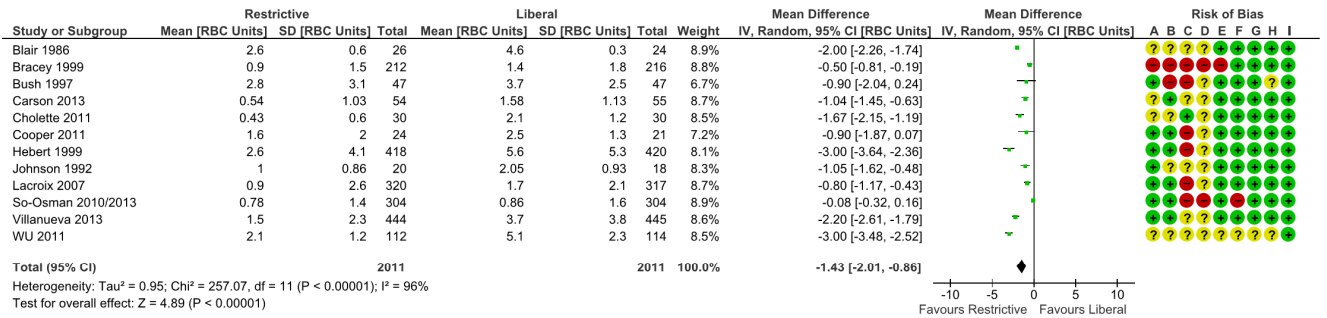
						Creatinine, R: 6/25, L: 5/25					hours, R: 5/25, L: 2/25; Hospital LOS >11 days, R: 9/25, L: 5/25
So-Osman 2010	(?), R: 1/299, L: 2/304	Composite complications, R: 99/299, L: 104/304	NA	NA	Cardiovascular complications , R: 34/299, L: 23/304	NA	Infections, R: 18/299 L: 31/304	NA	NA	Haemorrhage, R: 10/299, L: 12/305	Respiratory complications, R: 6/299, L: 15/304; Neuropsychiatric complications, R: 11/299, L: 13/304; Delayed mobilization, R: 22/299, L: 36/304
Villanueva 2013	45 day, R: 23/444, L: 41/445	Any adverse event, R: 179/444, L: 38/445	Fever, TACO or allergic reactions R: 14/444, L: 38/445	NA	ACS, pulmonary edema or arrhythmias, R: 49/444, L: 70/445	AKI, R: 78/444, L: 97/445	Bacterial infections, R: 119/444, L: 135/445	NA	Stroke/ TCI , R: 3/44, L: 6/445	Further bleeding, R: 45/444, L: 71/445	Pulmonary Complications, R: 48/444, L: 53/445
Walsh 2013	180 day, R: 19/51, L: 27/49; 30 day, R: 12/51, L: 16/49	NA	NA	ACS, R: 2/52, L: 2/49	NA	NA	NA	Any thrombotic event R: 6/51, L: 3/49; Pulmonary	Cerebral infarct, R: 0/51, L: 1/49	NA	ICU LOS, R: 24 (14-40)**, L: 23 (15-33); Hospital LOS, R: 34 (13-64)**, L: 31 (19-42);

								embolus, R: 0/51, L: 0/49; DVT, R: 1/51, L: 0/49; Other thrombotic events, R: 5/51, L: 2/49		Ventilation-free days at day 60, R: 38 (1-52)**, L: 27 (1-48); Antibiotic free days, R: 47 (36-53)**, L: 48 (41-53); SF-12 physical function score at day 180, R: 30 (24-40)**, L: 31 (24-39); SF-12 mental component score at day 180, R: 51 (31-57)**, L: 39 (34-57); Rivermead Mobility index 189, R: 13 (7-15)**, L: 10 (5-12)
Webert 2008	NA	NA	NA	NA	NA	NA	NA	NA	NA	Clinically significant bleeding, R: 22/29, L: 22/31;



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) Baseline imbalance
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