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.

| Study or Subgroup | Restrictive Events | Liberal Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias |
|-------------------|--------------------|----------------|--------------------------------|--------------------------------|--------------|
| Carson 1998       | 0                  | 2              | 0.9%                           | 0.20 [0.01, 4.04]               | ![Icon](A)    |
| Carson 2011       | 8                  | 1005           | 7.9%                           | 0.57 [0.24, 1.33]               | ![Icon](B)    |
| Foss 2009         | 6                  | 60             | 7.1%                           | 0.55 [0.22, 1.36]               | ![Icon](C)    |
| Gost-Bakker 2013  | 53                 | 5              | 5.2%                           | 1.22 [0.40, 3.76]               | ![Icon](D)    |
| Hebert 1999       | 42                 | 418            | 19.2%                          | 0.84 [0.57, 1.24]               | ![Icon](E)    |
| Lacoxo 2007       | 35                 | 79             | 19.9%                          | 0.44 [0.30, 0.63]               | ![Icon](F)    |
| Prick 2014        | 24                 | 211            | 14.2%                          | 1.08 [0.63, 1.87]               | ![Icon](G)    |
| Villeneuve 2013   | 44                 | 135            | 25.6%                          | 0.88 [0.72, 1.06]               | ![Icon](H)    |
| **Total (95% CI)**| **2555**           | **2552**       | **100.0%**                     | **0.73 [0.55, 0.98]**           | ![Icon](I)    |

Total events 240 318
Heterogeneity: Tau² = 0.07; Chi² = 14.91, df = 7 (P = 0.04); I² = 53%
Test for overall effect: Z = 2.13 (P = 0.03)

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

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0.01 0.1 1 10 100
Favours [experimental] Favours [control]
Appendix 2: Other adverse events, all trials

Transfusion reactions

| Study or Subgroup | Restrictive Events | Liberal Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----------------|---------------------------------|---------------------------------|--------------|
|                    | Total              | Total          |                                 |                                 |              |
|                    | 1709              | 1886           | 100.0%                          | 0.51 (0.33, 0.81)               |              |
| Total events       | 27                | 58             |                                 |                                |              |
| Heterogeneity:     | Tau² = 0.00; Chi² = 3.78, df = 4 (P = 0.44); I² = 0% |                                |                                |              |
| Test for overall effect: Z = 2.68 (P = 0.004) | | | | | |

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

| Study or Subgroup | Restrictive Events | Liberal Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----------------|---------------------------------|---------------------------------|--------------|
|                    | Total              | Total          |                                 |                                 |              |
|                    | 3357              | 3361           | 100.0%                          | 1.05 (0.81, 1.36)               |              |
| Total events       | 312               | 331            |                                 |                                |              |
| Heterogeneity:     | Tau² = 0.10; Chi² = 28.69, df = 13 (P = 0.007); I² = 55% |                                |                                |              |
| Test for overall effect: Z = 3.77 (P = 0.001) | | | | | |

Renal failure

| Study or Subgroup | Restrictive Events | Liberal Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias |
|-------------------|-------------------|----------------|---------------------------------|---------------------------------|--------------|
|                    | Total              | Total          |                                 |                                 |              |
|                    | 1258              | 1357           | 100.0%                          | 0.90 (0.64, 1.25)               |              |
| Total events       | 119               | 143            |                                 |                                |              |
| Heterogeneity:     | Tau² = 0.04; Chi² = 6.03, df = 5 (P = 0.25); I² = 25% |                                |                                |              |
| Test for overall effect: Z = 0.63 (P = 0.53) | | | | | |
## Infectious Complications

| Study or Subgroup | Restrictive Events Total | Liberal Events Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G H I |
|-------------------|--------------------------|----------------------|-------------------------------|-------------------------------|--------------------------------|
| Bracey 1999       | 5                         | 212                  | 2.0%                          | 1.70 [0.41, 7.02]              | ![Risk Icon](Risk Icon)       |
| Carson 1998       | 0                         | 42                   | 0.5%                          | 0.20 [0.01, 0.44]              | ![Risk Icon](Risk Icon)       |
| Carson 2011       | 8                         | 1007                 | 4.7%                          | 0.57 [0.24, 1.35]              | ![Risk Icon](Risk Icon)       |
| Carson 2013       | 2                         | 54                   | 0.5%                          | 5.09 [0.25, 103.64]            | ![Risk Icon](Risk Icon)       |
| Foss 2009         | 6                         | 60                   | 4.2%                          | 0.55 [0.22, 1.38]              | ![Risk Icon](Risk Icon)       |
| Gast-Bakker 2013  | 6                         | 53                   | 3.0%                          | 1.22 [0.40, 3.76]              | ![Risk Icon](Risk Icon)       |
| Grover 2006       | 3                         | 109                  | 1.3%                          | 0.67 [0.11, 3.91]              | ![Risk Icon](Risk Icon)       |
| Hajjar 2010       | 29                        | 249                  | 9.3%                          | 1.18 [0.17, 11.95]             | ![Risk Icon](Risk Icon)       |
| Hebert 1999       | 42                        | 418                  | 12.2%                         | 0.84 [0.57, 1.24]              | ![Risk Icon](Risk Icon)       |
| Lacroix 2007      | 35                        | 320                  | 13.3%                         | 0.44 [0.20, 0.65]              | ![Risk Icon](Risk Icon)       |
| Prick 2014        | 24                        | 211                  | 8.9%                          | 1.08 [0.63, 1.87]              | ![Risk Icon](Risk Icon)       |
| Robertson 2014    | 27                        | 99                   | 11.9%                         | 0.77 [0.51, 1.16]              | ![Risk Icon](Risk Icon)       |
| Shehata 2012      | 3                         | 25                   | 0.5%                          | 7.00 [0.38, 128.87]            | ![Risk Icon](Risk Icon)       |
| So-Osman 2010/2013 | 18                      | 299                  | 8.7%                          | 0.98 [0.34, 2.98]              | ![Risk Icon](Risk Icon)       |
| Villanueva 2013   | 119                       | 444                  | 18.2%                         | 0.88 [0.72, 1.09]              | ![Risk Icon](Risk Icon)       |

Total (95% CI) 3602 / 3615 100.0% 0.79 [0.64, 0.97]

| Total events | 326/416 |
|--------------|---------|
| Heterogeneity: Tau^2 = 0.05; Chi^2 = 23.17, df = 14 (P = 0.05); I^2 = 40% |
| Test for overall effect: Z = 2.22 (P = 0.03) |

## Thromboembolic events

| Study or Subgroup | Restrictive Events Total | Liberal Events Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G H I |
|-------------------|--------------------------|----------------------|-------------------------------|-------------------------------|--------------------------------|
| Carson 1998       | 1                         | 42                   | 1.8%                          | 3.00 [0.13, 71.61]             | ![Risk Icon](Risk Icon)       |
| Carson 2011       | 8                         | 1007                 | 23.2%                         | 0.67 [0.27, 1.62]              | ![Risk Icon](Risk Icon)       |
| Carson 2013       | 0                         | 54                   | 1.6%                          | 0.34 [0.01, 8.15]              | ![Risk Icon](Risk Icon)       |
| Foss 2009         | 1                         | 60                   | 3.3%                          | 0.50 [0.05, 5.37]              | ![Risk Icon](Risk Icon)       |
| Grover 2006       | 5                         | 60                   | 11.5%                         | 1.25 [0.30, 9.33]              | ![Risk Icon](Risk Icon)       |
| Lacroix 2007      | 4                         | 320                  | 9.7%                          | 0.99 [0.25, 3.93]              | ![Risk Icon](Risk Icon)       |
| Prick 2014        | 2                         | 226                  | 4.8%                          | 1.00 [0.14, 7.67]              | ![Risk Icon](Risk Icon)       |
| Robertson 2014    | 8                         | 99                   | 31.6%                         | 0.37 [0.07, 2.10]              | ![Risk Icon](Risk Icon)       |
| Shehata 2012      | 1                         | 26                   | 1.8%                          | 3.00 [0.13, 70.30]             | ![Risk Icon](Risk Icon)       |
| Walsh 2013        | 6                         | 51                   | 10.4%                         | 1.92 [0.51, 7.26]              | ![Risk Icon](Risk Icon)       |

Total (95% CI) 1944 / 1941 100.0% 0.73 [0.47, 1.12]

| Total events | 36/50 |
|--------------|-------|
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 7.96, df = 9 (P = 0.54); I^2 = 0% |
| Test for overall effect: Z = 1.46 (P = 0.15) |

## Stroke or Transitory cerebral ischemia

| Study or Subgroup | Restrictive Events Total | Liberal Events Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A B C D E F G H I |
|-------------------|--------------------------|----------------------|-------------------------------|-------------------------------|--------------------------------|
| Bracey 1999       | 11                        | 212                  | 12.9%                         | 1.25 [0.53, 2.94]              | ![Risk Icon](Risk Icon)       |
| Carson 1998       | 0                         | 42                   | 0.9%                          | 0.33 [0.01, 9.76]              | ![Risk Icon](Risk Icon)       |
| Carson 2011       | 3                         | 1007                 | 5.4%                          | 0.37 [0.15, 1.41]              | ![Risk Icon](Risk Icon)       |
| Carson 2013       | 0                         | 54                   | 0.9%                          | 0.34 [0.01, 8.15]              | ![Risk Icon](Risk Icon)       |
| Foss 2009         | 1                         | 60                   | 1.3%                          | 1.00 [0.06, 15.62]             | ![Risk Icon](Risk Icon)       |
| Hajjar 2010       | 15                        | 249                  | 9.3%                          | 1.02 [0.51, 2.03]              | ![Risk Icon](Risk Icon)       |
| Hebert 1999       | 25                        | 418                  | 37.8%                         | 0.76 [0.46, 1.26]              | ![Risk Icon](Risk Icon)       |
| Hotl 2014         | 7                         | 488                  | 10.4%                         | 0.70 [0.27, 1.71]              | ![Risk Icon](Risk Icon)       |
| Johnson 1992      | 1                         | 20                   | 1.0%                          | 2.71 [0.12, 62.70]             | ![Risk Icon](Risk Icon)       |
| Lacroix 2007      | 0                         | 320                  | 0.0%                          | 0.33 [0.01, 8.15]              | ![Risk Icon](Risk Icon)       |
| Robertson 2014    | 1                         | 99                   | 1.7%                          | 0.51 [0.05, 5.34]              | ![Risk Icon](Risk Icon)       |
| Shehata 2012      | 3                         | 25                   | 1.1%                          | 7.00 [0.38, 128.87]            | ![Risk Icon](Risk Icon)       |
| Villanueva 2013   | 3                         | 444                  | 5.0%                          | 0.50 [0.13, 1.99]              | ![Risk Icon](Risk Icon)       |
| Walsh 2013        | 0                         | 51                   | 0.9%                          | 0.32 [0.01, 7.68]              | ![Risk Icon](Risk Icon)       |

Total (95% CI) 3489 / 3498 100.0% 0.80 [0.59, 1.09]

| Total events | 70/88 |
|--------------|-------|
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 7.34, df = 13 (P = 0.08); I^2 = 0% |
| Test for overall effect: Z = 1.38 (P = 0.17) |
### Haemorrhagic events

| Study or Subgroup | Restrictive | Liberal | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias |
|-------------------|-------------|---------|--------|--------------------------------|--------------------------------|--------------|
| Blair 1986        | 1           | 12      | 20.91  | 0.10 [0.01, 0.75]              |                                |              |
| Hajjar 2010       | 13          | 249     | 11.25  | 1.20 [0.55, 2.63]              |                                |              |
| Holst 2014        | 147         | 488     | 148.94 | 1.00 [0.82, 1.20]              |                                |              |
| Lacoxo 2007       | 2           | 320     | 0.317  | 4.95 [0.24, 103.77]            |                                |              |
| Shehata 2012      | 5           | 25      | 2.25   | 2.50 [0.53, 11.70]             |                                |              |
| So-Osman 2010/2013| 10          | 299     | 12.35  | 0.85 [0.37, 1.94]              |                                |              |
| Villanueva 2013   | 45          | 444     | 71.45  | 0.64 [0.45, 0.96]              |                                |              |
| Webert 2008       | 25          | 29      | 28.99  | 0.95 [0.79, 1.16]              |                                |              |
| Total (95% CI)    | 1880        | 1809    | 100.0% | 0.90 [0.71, 1.14]              |                                |              |

Total events: 248/281

Heterogeneity: Tau² = 0.04; Chi² = 13.49, df = 7 (P = 0.06); I² = 48%

Test for overall effect: Z = 0.90 (P = 0.37)
| Trial ID       | Mortality 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 |
| 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 |
| 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 | Neurological 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 |
| Carson 1998   | 60 day, R: 5/42, L: 2/42 | NA | NA | MI, R: 0/42, L: 0/42 | 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: |
|    | 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 | MI, R: 38/1008, L: 23/1005 | Congestive heart disease, R: 35/1007, L: 27/1005 | 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 2011 | 30 day, R: 7/54, L: 1/55 | Death/MI/unscheduled revascularisation/unscheduled cardiac admission, R: 17/54, L: 9/55 | 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 | Pneumonia R: 2/54, L: 0/55 | Thromboembolic events, R: 0/54, L: 1/55 | Stroke, R: 0/54, L: 1/55 | NA |
| Carson 2013 | 30 day, R: 2/24, L: 1/21 | Death/recurrent MI, or new/worsening HF, or recurrent ischemia, R: 13/24, | Recurrent in-hospital ischemia, R: 1/24, L: 0/21 | NA | NA | NA | NA | NA |
| Cooper 2011 | 30 day, R: 7/54, L: 1/55 | Death/MI/unscheduled revascularisation/unscheduled cardiac admission, R: 17/54, L: 9/55 | 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 | Pneumonia R: 2/54, L: 0/55 | Thromboembolic events, R: 0/54, L: 1/55 | Stroke, R: 0/54, L: 1/55 | NA |
| Cooper 2013 | 30 day, R: 2/24, L: 1/21 | Death/recurrent MI, or new/worsening HF, or recurrent ischemia, R: 13/24, | Recurrent in-hospital ischemia, R: 1/24, L: 0/21 | NA | NA | NA | NA | In-hospital death, recurrent MI, or new or worsening HF at day 30, R: 5/24, L: 13/21 |
| Study            | Complications | Respiratory tract infections | Mechanical ventilation time (hrs) | LOS PICU (days) | LOS Hospital (days) | Cost per patient | Mean arterial lactate levels (mM) | Peak arterial lactate levels (mM) |
|------------------|----------------|-----------------------------|-----------------------------------|-----------------|-------------------|-----------------|-----------------------------------|-----------------------------------|
| Gast-Bakker 2013 | NA             | NA                          | NA                                | NA              | NA                | NA              | NA                                | NA                                |
|                  | Overall        |                             | NA                                | NA              | NA                | NA              | NA                                | NA                                |
|                  | complications  |                             | NA                                | NA              | NA                | NA              | NA                                | NA                                |
|                  | in ICU         |                             | NA                                | NA              | NA                | NA              | NA                                | NA                                |
|                  | R: 15/53,      |                             | R: 6/53                           | R: 20 (9-52)**  | NA                | NA              | NA                                | NA                                |
|                  | L: 11/54       |                             | L: 5/54                           | L: 16 (9-27)    | NA                | NA              | NA                                | NA                                |
| Gregersen 2013   | 90 day         | R: 35%                       | L: 20%                            | R: 2 (1-4)**    | L: 2 (1-5)       | NA              | NA                                | NA                                |
|                  | at discharge   |                             | NA                                | R: 8 (7-11)     | L: 9 (7-14)       | NA              | NA                                | NA                                |
| Cholette 2011    | At discharge   |                             | NA                                | R: 0/30         | L: 1/30           | NA              | NA                                | NA                                |
|                  | R: 0/30,       |                             | NA                                | NA              | NA                | NA              | NA                                | NA                                |
|                  | L: 1/30        |                             | NA                                | NA              | NA                | NA              | NA                                | NA                                |
| Fortune          | NA             | NA                          | NA                                | NA              | NA                | NA              | NA                                | NA                                |
|                  | NA             | NA                          | NA                                | NA              | NA                | NA              | NA                                | NA                                |
|                  | NA             | NA                          | NA                                | NA              | NA                | NA              | NA                                | NA                                |
| Year | Study | Timeframe | Any Cardiac Event | Silent MI | LBBB\(†\) | Any Cardiac Event\(‡\) | Any Infectious Complications | Thromboembolic Event | Cerebrovascular Event | Any Neurological Complications | Abscess | Pulmonary Edema/Congestive Heart Disease |
|------|-------|-----------|------------------|-----------|-----------|------------------------|-----------------------------|----------------------|--------------------------|----------------------------|---------|------------------------------------------|
| 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; Any Inflammatory Complications, R: 6/60, L: 11/60; Sepsis, R: 1/60, L: 1/60 | | Thromboembolic Event, R: 1/60, L: 2/60 | | | | | Pulmonary Edema/Congestive Heart Disease, R: 1/60, L: 1/60; |
| 2005 | Grover | 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; | | 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; | | | | | | |
| 2010 | Hajjar | 30 day, R: 15/249, L: 12/253 | Any Cardiac Event\(‡\), R: 59/249, L: 53/253 | NA | Any Cardiac Event\(‡\), R: 59/249, L: 53/253; Cardiogenic Shock, R: 22/249, L: 12/253 | AKI Requiring Dialysis or Hemofiltration, R: 29/249, L: 25/253 | Infectious Complications, R: 15/249, L: 15/253 | Neurological Complications, R: 13/249, L: 11/253 | Bleeding, R: 5/249, L: 2/253 | | |

\(†\): LBBB indicates left bundle branch block.

\(‡\): Any cardiac event includes MI, any cardiac complication, and any cardiac death.

\(‡‡\): Any cardiac event includes MI, any cardiac complication, any cardiac death, any myocardial infarction, and any cardiac event.
| Study | Follow-up | Event | Multiple organ failure (>3 organs) | Rm | Lm | NA | NA | NA | NA | NA | NA |
|-------|-----------|-------|----------------------------------|----|----|----|----|----|----|----|----|----|
| Hebert 1995 | 120 day, R: 13/33, L: 11/36; 30 day, R: 8/33, L: 9/36 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Holst 2014 | 90 day all cause, R: 216/502, L: 223/496 | NA | Acute haemolytic reaction, R: 0/488, L: 1/489 | ML, R: 17/488, L: 6/489 | 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 | Cerbrovascular accidents and encephalopathies, R: 25/418, L: 33/420 | 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 |
| Johnsson 1992 | NA | NA | Perioperative MI, R: 0/20, L: 1/18 | Arrhythmias, R: 4/20, L: 6/18 | 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; Postpericardio my syndrome, R: 1/18, L: 1/20 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lacroix 2007** | NA | NA | 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 | 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 |
| Study    | Outcome            | R Count | L Count | Notes                                                                 |
|----------|--------------------|---------|---------|----------------------------------------------------------------------|
| Lotke 1999 | Serious adverse events | 19/320  | 19/317  | R: 16/62, L: 5/65; MI, R: 1/62, L: 0/65; Dysrhythmia, R: 1/62, L: 0/65 |
|          | NA                 | NA      | NA      | MI, R: 1/62, L: 0/65; Dysrhythmia, R: 1/62, L: 0/65; 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 | Total hospital LOS | 23.3    | 21.8    | 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      | 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 |
|          | Total infectious complications | 24/211  | 22/209  | R: 24/211, L: 22/209; Infected, Thromboembolic event, R: 2/226, L: 2/227 |
| Prick 2012 | Total infectious complications | 3/225   | 5/228   | R: 0/30, L: 3/227; Endometritis, R: 3/225, L: 5/228 |
| Years | Event Type | Number of Events | Left | Right |
|-------|------------|------------------|------|-------|
| Roberts 2014 | 180 day | 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 thromboembolic event, R: 8/99, L: 22/101; Pulmonary embolus, R: 1/99, L: 6/101 | Stroke, R: 1/99, L: 2/101 |
| Shehata 2012 | 30 day all cause | Composite score, R: 14/25, L: 8/25 | Transfusion reactions, R: 0/25, L: 0/25 | 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 |
| Study          | Timeframe | Composite complications, R: 99/299, L: 104/304 | Creatinine, R: 6/25, L: 5/25 | Cardiovascular complications, R: 34/299, L: 23/304 | Infections, R: 18/299, L: 31/304 | Haemorrhage, R: 10/299, L: 12/305 | Respiratory complications, R: 6/299, L: 15/304; Neurropsychiatric complications, R: 11/299, L: 13/304; Delayed mobilization, R: 22/299, L: 36/304 |
|---------------|-----------|-----------------------------------------------|-----------------------------|-----------------------------------------------|------------------------------------|-----------------------------------|----------------------------------------------------------------------------------|
| So-Osman 2010 | 45 day, R: 23/444, L: 41/445 | Any adverse event, R: 179/444, L: 38/445 | NA                          | NA                                            | NA                                 | NA                                | NA                                                                                |
| Villanueva 2013 | 180 day, R: 19/51, L: 27/49; 30 day, R: 12/51, L: 16/49 | ACS, pulmonary edema or arrhythmias, R: 49/444, L: 70/445 | ACS, pulmonary edema or arrhythmias, R: 49/444, L: 70/445 | Bacterial infections, R: 119/444, L: 135/445 | NA                                 | NA                                | NA                                                                                |
| Walsh 2013 | 180 day, R: 24 (14-40)**, L: 23 (15-33); Hospital LOS, R: 34 (13-64)**, L: 31 (19-42); ICU LOS, R: 24 (14-40)**, L: 23 (15-33); Hospital LOS, R: 34 (13-64)**, L: 31 (19-42); | Any thrombotic event, R: 6/51, L: 3/49; Pulmonary | Any thrombotic event, R: 6/51, L: 3/49; Pulmonary | Any thrombotic event, R: 6/51, L: 3/49; Pulmonary | Any thrombotic event, R: 6/51, L: 3/49; Pulmonary | Any thrombotic event, R: 6/51, L: 3/49; Pulmonary | NA                                                                                |
| Webert 2008 | NA | NA | NA | NA | NA | NA | NA | NA | NA | Clinically significant bleeding, R: 22/29, L: 22/31; |
|-------------|----|----|----|----|----|----|----|----|----|-----------------------------|
|             |    |    |    |    |    |    |    |    |    | 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) |
| Study   | 30 day all cause, R: 3/112, L: 4/114 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
|---------|------------------------------------|----|----|----|----|----|----|----|----|----|----|----|----|
| WU 2011 | Any bleeding event, R: 25/29, L: 28/31 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Zygun 2009 | ICU, R: 3/20, L: 0/10 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Study or Subgroup | Restrictive Events | Liberal Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI | Risk of Bias A | B | C | D | E | F | G | H | I |
|------------------|-------------------|----------------|-------------------------------|-------------------------------|----------------|---|---|---|---|---|---|---|---|---|
| Blair 1988       | 5                 | 26             | 24                            | 2.1%                          | 0.21 [0.10, 0.44] |   | * |   | * |   |   |   |   |   |
| Bravos 1999      | 42                | 212            | 80                            | 4.0%                          | 0.53 [0.39, 0.74] |   | * |   | * |   |   |   |   |   |
| Bush 1997        | 40                | 50             | 43                            | 4.6%                          | 0.91 [0.77, 1.08] |   | * |   | * |   |   |   |   |   |
| Carson 1998      | 19                | 42             | 42                            | 3.9%                          | 0.46 [0.33, 0.64] |   | * |   | * |   |   |   |   |   |
| Carson 2011      | 413               | 1007           | 970                           | 1003                          | 4.2 [0.39, 0.46] |   | * |   | * |   |   |   |   |   |
| Choksi 2011      | 19                | 30             | 39                            | 4.2%                          | 0.68 [0.50, 0.87] |   | * |   | * |   |   |   |   |   |
| Cooper 2011      | 13                | 24             | 21                            | 3.8%                          | 0.55 [0.38, 0.80] |   | * |   | * |   |   |   |   |   |
| Foss 2009        | 22                | 60             | 44                            | 6.0%                          | 0.50 [0.35, 0.72] |   | * |   | * |   |   |   |   |   |
| Grover 2006      | 37                | 109            | 46                            | 109                           | 0.80 [0.57, 1.13] |   | * |   | * |   |   |   |   |   |
| Hajjar 2010      | 118               | 249            | 198                           | 253                           | 0.51 [0.32, 0.70] |   | * |   | * |   |   |   |   |   |
| Hebert 1995      | 18                | 33             | 35                            | 36                            | 0.56 [0.41, 0.77] |   | * |   | * |   |   |   |   |   |
| Hebert 1999      | 280               | 418            | 420                           | 420                           | 0.67 [0.63, 0.73] |   | * |   | * |   |   |   |   |   |
| Holst 2014       | 312               | 486            | 483                           | 489                           | 0.85 [0.61, 0.99] |   | * |   | * |   |   |   |   |   |
| Johnson 1992     | 15                | 20             | 18                            | 18                            | 0.76 [0.58, 0.99] |   | * |   | * |   |   |   |   |   |
| Lacnose 2007     | 146               | 320            | 310                           | 317                           | 0.47 [0.41, 0.53] |   | * |   | * |   |   |   |   |   |
| Labke 1999       | 16                | 62             | 65                            | 65                            | 0.26 [0.17, 0.40] |   | * |   | * |   |   |   |   |   |
| Parker 2013      | 11                | 100            | 100                           | 100                           | 0.11 [0.07, 0.20] |   | * |   | * |   |   |   |   |   |
| Pick 2014        | 33                | 261            | 251                           | 258                           | 0.13 [0.09, 0.18] |   | * |   | * |   |   |   |   |   |
| Robertson 2014   | 52                | 99             | 73                            | 101                           | 0.73 [0.58, 0.91] |   | * |   | * |   |   |   |   |   |
| Shehata 2012     | 13                | 25             | 22                            | 25                            | 0.59 [0.39, 0.88] |   | * |   | * |   |   |   |   |   |
| So-Oman 2012/2013| 139               | 299            | 119                           | 304                           | 0.93 [0.76, 1.14] |   | * |   | * |   |   |   |   |   |
| Villarvuna 2013  | 219               | 444            | 384                           | 445                           | 0.57 [0.52, 0.63] |   | * |   | * |   |   |   |   |   |
| Walsh 2013       | 40                | 51             | 49                            | 49                            | 0.79 [0.68, 0.91] |   | * |   | * |   |   |   |   |   |
| Webet 2008       | 26                | 29             | 29                            | 31                            | 0.96 [0.82, 1.12] |   | * |   | * |   |   |   |   |   |

Total (95% CI) 4458 4466 100.0% 0.54 [0.47, 0.63]  

Total events 3008 3855   

Heterogeneity: Tau² = 0.11; CH² = 431.32, df = 23 (P < 0.00001); I² = 95%  

Test for overall effect: Z = 8.31 (P < 0.00001)  

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
| Study or Subgroup | Mean (RBC Units) | Weight | Mean Difference | Risk of Bias |
|-------------------|---------------|--------|----------------|-------------|
| **Restrictive**    |               |        |                |             |
| Bracey 1999       | 2.6          | 0.06   | -2.00 [2.29, -1.75] | *           |
| Bush 1997         | 3.9          | 0.14   | -0.99 [2.04, -0.24] |             |
| Carson 2013       | 0.54         | 1.03   | -0.64 [1.46, -0.63] | *           |
| Chaleke 2011      | 0.43         | 0.06   | -0.87 [2.15, -1.10] | *           |
| Cooper 2011       | 1.6          | 2.24   | -0.69 [1.17, -0.07] | *           |
| Hebert 1999       | 2.6          | 4.11   | -3.00 [3.04, -2.30] | *           |
| Johnson 2002      | 1            | 0.06   | -0.93 [2.41, -0.56] | *           |
| Lacroix 2007      | 0.9          | 2.62   | -0.60 [1.17, -0.43] | *           |
| Sn-Dahman 2010/2013| 0.75       | 1.44   | -1.16 [2.32, -5.10] | *           |
| Villanueva 2013   | 1.5          | 2.34   | -2.20 [2.61, -1.79] | *           |
| Wu 2011           | 1            | 1.72   | -2.50 [2.44, -0.52] | *           |
| **Liberal**       |               |        |                |             |

Heterogeneity: Tau^2 = 0.95; CH^2 = 257.07, df = 11 (P < 0.00001); I^2 = 96%

Test for overall effect: Z = 4.69 (P = 0.00001)

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 imbalances (baseline bias)
(H) Sponsor bias
(I) Academic bias