Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTABLE 1. Search Strategy

Search Strategy in Ovid MEDLINE
1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.
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*)).mp.
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.
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.
12. (transfus* adj5 (restrict* or liberal*)).mp.
13. ((blood or transfus*) adj3 (management or program*)).mp.
14. 8 or 9 or 10 or 11 or 12 or 13
15. randomi?ed.ab,ti.
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. placebo.ab.
19. clinical trials as topic.sh.
20. randomly.ab.
21. trial.ti.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. (animals not (humans and animals)).sh.
24. 22 not 23
25. 24 and 14

eTABLE 2. RBC Use and Baseline Hemoglobin in Study Groups

Source	RBC Use in Restrictive Group	RBC Use in Liberal Group	Baseline Hemoglobin in Restrictive Group (g/dL)	Baseline Hemoglobin in Liberal Group (g/dL)
Cardiac Patients				
Bracey et al, 1999[20]	Mean RBC units: 2.0 (SD 2.2); 127 (60%) of patients received RBC transfusion	Mean RBC units: 2.5 (SD 2.6); 138 (64%) of patients received RBC transfusion	Mean Hb: 14.2 (SD 1.2)	Mean Hb: 14.3 (SD 1.2)
Hajjar et al, 2010[21]	Median RBC units: 0 (IQR 0-2) 258 RBC units, total; 117 (47%) of patients received RBC transfusion	Median RBC units: 2 (IQR 1-3) 613 RBC units, total; 197 (78%) of patients received RBC transfusion	Mean Hb: 13.4 (SD 1.8)	Mean Hb: 13.1 (SD 1.6)
Cholette et al, 2011[22]	Mean RBC units: 0.43 (SD 0.6); 11 (37%) of patients received RBC transfusion	Mean RBC units: 2.1 (SD 1.2); 29 (97%) of patients received RBC transfusion	Mean Hb: 14.6 (SD 1.8)	Mean Hb: 14.6 (SD 1.7)
Cooper et al, 2011[23]	Mean RBC units: 1.6 (SD 2.0); 13 (54%) of patients received RBC transfusion	Mean RBC units: 2.5 (SD 1.3); 21 (100%) of patients received RBC transfusion	Mean Hct: 27.5% (SD 2.4%) [Hb 9.2 g/dL]	Mean Hct: 26.9% (SD 1.9%) [Hb 9.0 g/dL]
Shehata et al, 2012[24]	50 RBC units, total; 13 (52%) of patients received RBC transfusion	99 RBC units, total; 22 (88%) of patients received RBC transfusion	Graphed only.	Graphed only.
Carson et al, 2013[10]	27 RBC units, total; Mean RBC units: 0.49 (SD 1.03); 15 (27%) of patients received RBC transfusion	87 RBC units, total; Mean RBC units: 1.58 (SD 1.13); 52 (95%) of patients received RBC transfusion	Mean Hb: 8.97 (SD 0.73)	Mean Hb: 9.18 (SD 0.64)
de Gast-Bakker et al, 2013[25]	Mean RBC volume 186 ml (SD 70) per patient	Mean RBC volume 258 ml (SD 87) per patient	Mean Hb: 12.2 (SD 1.2)	Mean Hb: 11.9 (SD 1.5)
Critical Care Patients				
Hebert et al, 1999[26]	Mean RBC units: 2.6 (SD 4.1); 280 (67%) of patients received RBC transfusion	Mean RBC units: 5.6 (SD 5.3); 420 (100%) of patients received RBC transfusion	Mean Hb: 8.2 (SD 0.7)	Mean Hb: 8.2 (SD 0.7)
LaCroix et al, 2007[27]	146 (46%) of patients received RBC transfusion	310 (98%) of patients received RBC transfusion	Mean Hb: 8.0 (SD 1.0)	Mean Hb: 8.0 (SD 0.9)

Gastrointestinal Bleeding				
Villanueva et al, 2013[11]	Median RBC units: 0 (Range 0-19); 671 RBC units, total; 219 (49%) of patients received RBC transfusion	Median RBC units: 3 (Range 0-36); 1638 RBC units, total; 384 (86%) of patients received RBC transfusion	Mean Hb: 9.6 (SD 2.2)	Mean Hb: 9.4 (SD 2.4)
Low Birthweight				
Kirpalani et al, 2006[28]	Mean RBC units: 4.9 (SD 4.2); 1091 RBC units, total; 199 (89%) of patients received RBC transfusion	Mean RBC units: 5.7 (SD 5.0); 1305 RBC units, total; 217 (95%) of patients received RBC transfusion	Mean Hb: 16.4 (SD 2.5)	Mean Hb: 16.5 (SD 2.3)
Orthopedics				
Carson et al, 1998[29]	Median RBC units: 0 (IQR 0-2); 19 (45%) of patients received RBC transfusion	Median RBC units: 2 (IQR 1-2); 41 (98%) of patients received RBC transfusion	Mean Hb: 9.1 (SD 0.6)	Mean Hb: 9.1 (SD 0.6)
Grover et al, 2006[30]	Median RBC units: 0 (Range 0-5) 89 RBC units, total; 37 (34%) of patients received RBC transfusion	Median RBC units: 0 (Range 0-19) 119 RBC units, total; 46 (43%) of patients received RBC transfusion	Mean Hb: 13.1 (SD 1.2)	Mean Hb: 13.6 (SD 1.2)
Foss et al, 2009[31]	Median RBC units: 1 (IQR 1-2); 22 (37%) of patients received RBC transfusion	Median RBC units: 2 (IQR 1-2); 44 (74%) of patients received RBC transfusion	Graphed but not stated.	Graphed but not stated.
So-Osman et al, 2010[32]	Mean 0.78 RBC units/patient (SD 1.4). Overall, 105 (35%) of patients received RBC transfusion.	Mean 0.86 RBC units/patient (SD 1.6). Overall, 93 (31%) of patients received RBC transfusion.	Mean Hb: 13.7 (SD 1.4)	Mean Hb: 13.7 (SD 1.4)
Carson et al, 2011[33]	Median RBC units: 0 (IQR 0-1); 652 RBC units, total; 413 (41%) of patients received RBC transfusion	Median RBC units: 2 (IQR 1-2); 1866 RBC units, total; 970 (97%) of patients received RBC transfusion	Mean Hb: 11.3 (SD 1.5) before surgery	Mean Hb: 11.3 (SD 1.5) before surgery
Gregersen et al, 2012[14]	Not stated.	Not stated.	Not stated.	Not stated.

Postpartum				
Prick et al, 2014[34]	Median RBC units: 0 (IQR 0-0). 88 RBC units, total. 33 (13%) of patients received RBC transfusion	Median RBC units: 2 (IQR 2-2). 517 RBC units, total. 251 (97%) of patients received RBC transfusion	Median Hb: 7.4 (IQR 6.8–7.7)	Median Hb: 7.3 (IQR 6.8–7.7)
Sepsis				
Karam et al, 2011[35]	39 (56%) of patients received RBC transfusion	67 (99%) of patients received RBC transfusion	Mean Hb: 7.9 (SD 1.0)	Mean Hb: 7.8 (SD 0.9)
Sickle Cell				
Vichinsky et al, 1995[36]	Mean RBC units: 2.5	Mean RBC units: 5.0	Mean Hb: 7.9 Median Hb S: 59%	Mean Hb: 8 Median Hb S: 31%
Howard et al, 2013[37]	38 RBC units, total	71 RBC units, total	Median Hb: 77 (IQR 71–84)	Median Hb: 80 (IQR 74–86)

Abbreviations: Hb = hemoglobin, Hct = hematocrit, RBC = red blood cell, g = gram, dL = deciliter, SD = standard deviation, IQR = interquartile range.

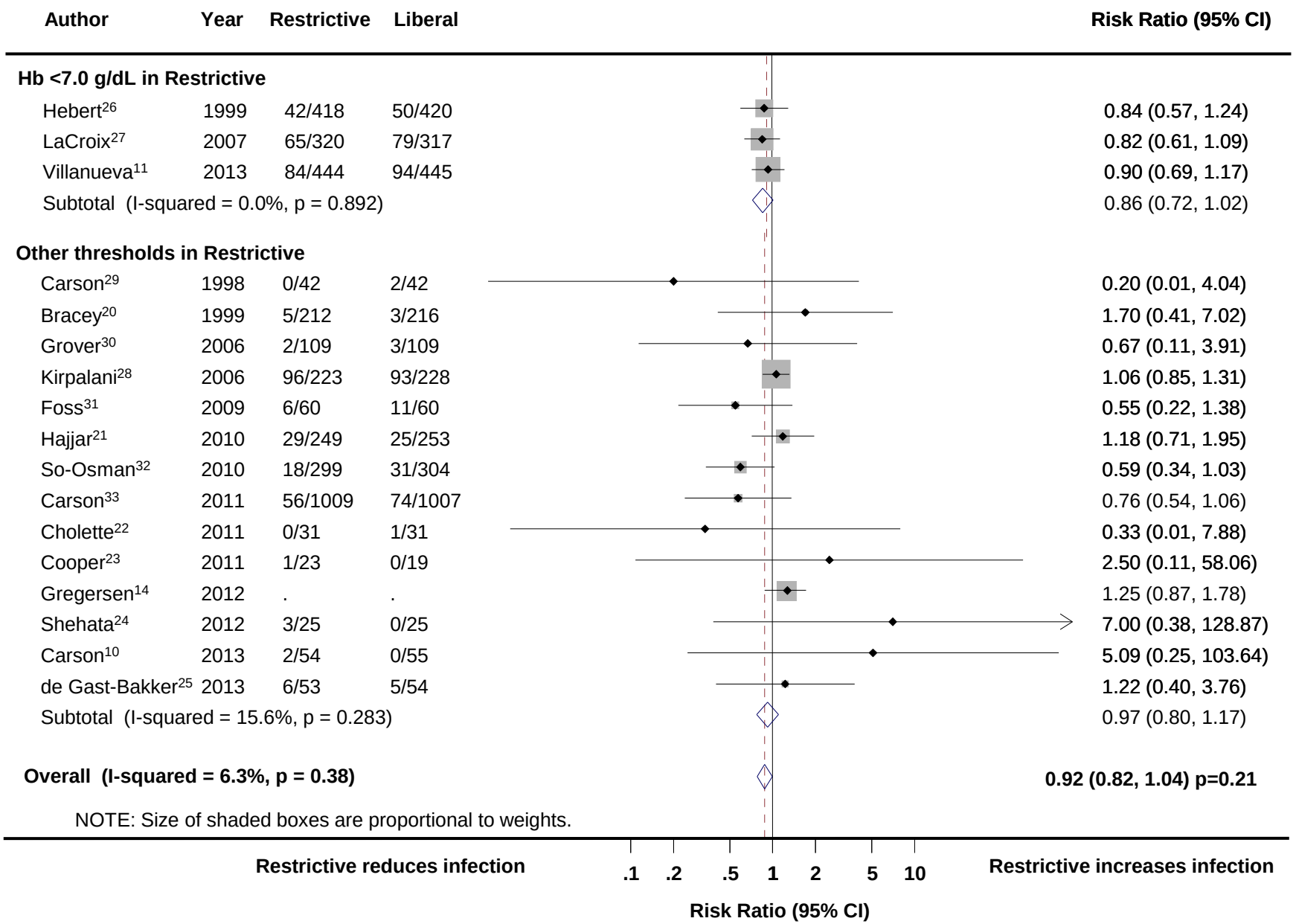
eTABLE 3. Assessment of Study Quality

Source	Concealed Randomization	Blinding	Withdrawals	Protocol Violations
Cardiac Patients				
Bracey et al, 1999[20]	Not stated.	Not stated.	None stated.	None stated.
Hajjar et al, 2010[21]	Concealed.	Patients and outcome assessors were blinded to study assignment.	10 exclusions after randomization (no surgery).	None stated.
Cholette et al, 2011[22]	Not stated.	Surgeon, anesthesiologist, perfusionist operating room staff, and independent data safety monitor were blinded to study assignment.	2 exclusions after randomization (no surgery).	100% compliance.
Cooper et al, 2011[23]	Concealed.	No blinding.	3 patients lost to 30 day follow-up (1 in restrictive arm and 2 in liberal arm).	Patients could receive RBC transfusion at the discretion of the treating physician due to active bleeding, persistent hypotension related to hypovolemia, active ischemia, and if it was in the patient's best interest. Once resolved, transfusion was again given according to protocol. In addition, 1 patient in each arm received a transfusion when Hct was above threshold.
Shehata et al, 2012[24]	Concealed.	Not blinded.	None.	16% protocol violations in restrictive group and 59% violations in the liberal group.
Carson et al, 2013[10]	Not stated.	Outcomes were classified with blinded treatment assignment.	1 loss to follow-up.	6 protocol violations.
de Gast-Bakker et al, 2013[25]	Not stated.	No blinding.	None.	7 protocol violations.

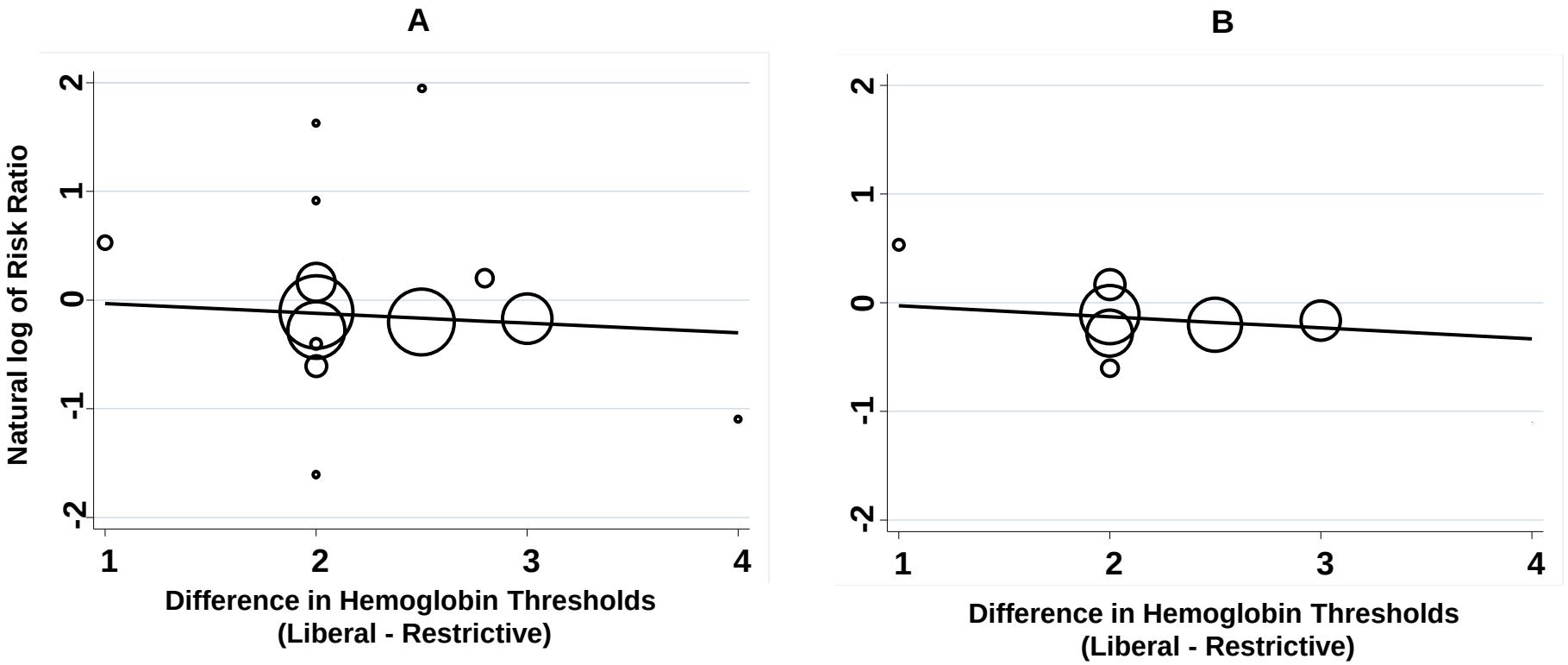
Critical Care Patients				
Hebert et al, 1999[26]	Concealed.	Not blinded.	9 withdrawals. 3 lost to follow-up at 60 days.	Protocol violations for 24 patients.
LaCroix et al, 2007[27]	Concealed.	Statistician and members of the data and safety monitoring committee were blinded to study assignment.	11 withdrawals.	11 protocol violations.
Gastrointestinal Bleeding				
Villanueva et al, 2013[11]	Concealed.	Not blinded.	4 withdrawals. 23 excluded after randomization.	54 protocol violations.
Low Birthweight				
Kirpalani et al, 2006[28]	Concealed.	Not blinded.	None.	Not stated.
Orthopedics				
Carson et al, 1998[29]	Concealed.	Study nurses were blinded to study assignment. Study nurses obtained data for outcomes.	3 withdrawals.	5 protocol violations.
Grover et al, 2006[30]	Concealed.	Patients and technicians analyzing the primary outcome were blinded to study assignment.	No withdrawals.	Not stated.
Foss et al, 2009[31]	Concealed.	Patients and physiotherapists conducting the outcome assessments were blinded to study assignment.	13 excluded after randomization.	Not stated.
So-Osman et al, 2010[32]	Concealed.	Investigators were blinded to study assignment.	16 excluded after randomization. None lost to follow-up.	NOTE: A complicated transfusion strategy yielded results such that, in 2 hospitals the new protocol was more restrictive, but In 1 hospital, the new protocol was more liberal.
Carson et al, 2011[33]	Concealed.	Nurses who were blinded to study assignment obtained outcome data after hospital discharge.	14 withdrawals. 2 lost to follow-up. 1 incomplete follow-up.	91 (9%) in liberal group. 56 (5.6%) in restrictive group.

Gregersen et al, 2012[14]	Not stated.	Not stated.	Not stated.	Not stated.
Postpartum				
Prick et al, 2014[34]	Concealed.	Not blinded.	2 withdrawals.	40 protocol violations.
Sepsis				
Karam et al, 2011[35]	Concealed.	Statistician and members of the data and safety monitoring committee were blinded to study assignment.	None.	17 patients were temporarily suspended from the transfusion protocol.
Sickle Cell				
Vichinsky et al, 1995[36]	Not stated.	Not stated.	88 operations excluded after randomization.	Not stated.
Howard et al, 2013[37]	Concealed.	Not blinded.	12 withdrawals.	4 protocol violations

eFIGURE 1. Forest Plot of Risk Ratios for Infection Comparing Restrictive versus Liberal Transfusion Strategies by Hemoglobin Threshold



eFIGURE 2. Difference in Hemoglobin Thresholds in Study Groups Regressed on the Natural Log of the Risk Ratio of Infection



LEGEND

A: Results for 15 trials with infection (serious infections and selected infections) recorded as an outcome.

B: Results for 7 trials with all serious infections as an outcome.