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Red Blood Cell Transfusion
2023 AABB International Guidelines

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IMPORTANCE Red blood cell transfusion is a common medical intervention with benefits and harms.

OBJECTIVE To provide recommendations for use of red blood cell transfusion in adults and children.

EVIDENCE REVIEW Standards for trustworthy guidelines were followed, including using Grading of Recommendations Assessment, Development and Evaluation methods, managing conflicts of interest, and making values and preferences explicit. Evidence from systematic reviews of randomized controlled trials was reviewed.

FINDINGS For adults, 45 randomized controlled trials with 20 599 participants compared restrictive hemoglobin-based transfusion thresholds, typically 7 to 8 g/dL, with liberal transfusion thresholds of 9 to 10 g/dL. For pediatric patients, 7 randomized controlled trials with 2730 participants compared a variety of restrictive and liberal transfusion thresholds. For most patient populations, results provided moderate quality evidence that restrictive transfusion thresholds did not adversely affect patient-important outcomes. Recommendation 1: for hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). In accordance with the restrictive strategy threshold used in most trials, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for those undergoing orthopedic surgery or those with preexisting cardiovascular disease. Recommendation 2: for hospitalized adult patients with hematologic and oncologic disorders, the panel suggests a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (conditional recommendations, low certainty evidence). Recommendation 3: for critically ill children and those at risk of critical illness who are hemodynamically stable and without a hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). Recommendation 4: for hemodynamically stable children with congenital heart disease, the international panel suggests a transfusion threshold that is based on the cardiac abnormality and stage of surgical repair: 7 g/dL (biventricular repair), 9 g/dL (single-ventricle palliation), or 7 to 9 g/dL (uncorrected congenital heart disease) (conditional recommendation, low certainty evidence).

CONCLUSIONS AND RELEVANCE It is good practice to consider overall clinical context and alternative therapies to transfusion when making transfusion decisions about an individual patient.

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Supplemental content

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Red blood cell (RBC) transfusion is a common and costly treatment; approximately 118 million units of blood are collected worldwide each year.[1,2] Clinicians should offer RBC transfusion to patients only when benefits outweigh harms. Harms include infectious and noninfectious complications; although serious reactions are infrequent, there remains potential for substantial harm (**Table 1**).[3,4] Patient advocacy groups support minimizing harms by avoiding transfusions without clear benefit.[5]

Although the average acquisition cost of a unit of RBCs is $215 in the United States,[6,7] it varies by country and region. Acquisition costs do not typically cover expenses of distribution, storage, processing, administration, and monitoring for complications.[7,8] Many blood transfusion providers face challenges, exacerbated by the COVID-19 pandemic, in maintaining adequate stocks of RBCs.[9]

Randomized controlled trials (RCTs) assessing outcomes of different transfusion thresholds typically compare higher hemoglobin thresholds (liberal transfusion strategy) with lower ones (restrictive transfusion strategy) for RBC transfusions. The numbers of these trials continue to increase. AABB guidelines in 2012 included 19 RCTs; in 2016, 31 RCTs.[10,11] In 2018, the Transfusion and Anemia Expertise Initiative published guidelines based on 5 RCTs for RBC transfusion in critically ill children.[12] In 2021, an updated Cochrane systematic review included 48 trials.[13] Given the expanded evidence base and the prior absence of AABB guidelines specific to children, we reexamined the transfusion threshold evidence and provide updated guidance.

Guideline Development Process

The AABB commissioned and funded updated guidelines through the AABB Clinical Transfusion Medicine Committee. To encourage wide implementation of the recommendations, the board of directors supported recruiting experts in RBC transfusion from international professional organizations (eAppendix in the Supplement). These recommendations were developed in collaboration with and are endorsed by the International Society of Blood Transfusion, International Collaboration for Transfusion Medicine Guidelines, the Society of Critical Care Medicine, the European Blood Alliance, and the Society for the Advancement of Patient Blood Management.

These guidelines follow existing standards of trustworthiness,[14] including use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for summarizing evidence and moving from evidence to recommendations[15] to provide credible recommendations for clinicians caring for adults and children considered for RBC transfusions. These guidelines do not address transfusion in preterm neonates.

Perspective

The panel chose individual patients as the primary perspective but also considered public health considerations; for example, supply of blood.

Panel Composition and Conflicts

The international panel included members with expertise in transfusion medicine, supported by a GRADE methodologist (G.G.) and a patient partner (A.D.) (eAppendix in the Supplement). In accordance with AABB policy, individual members disclosed all potential financial, professional, or personal conflicts of interest; none had substantive conflicts.[16] Five members were authors of trials included in a systematic review on transfusion thresholds (J.L.C., S.J.S., Y.L., C.S.-O., and E.M.W.) and did not vote on corresponding recommendations.

Table 1. Approximate Per-Unit Risk for Red Blood Cell (RBC) Transfusion in the US[a]

Adverse event	Approximate risk per RBC transfusion
Febrile reaction	1:161[3]
Allergic reaction	1:345[3]
Transfusion-associated circulatory overload	1:125[3]
Transfusion-related acute lung injury	1:1250[3]
Anaphylactic reactions	1:5000[3]
Hepatitis B virus	1:1 100 000[4]
Hepatitis C virus	1:1 200 000[4]
HIV	1:1 600 000[4]

[a] The incidence of noninfectious complications of transfusion reactions is based on active surveillance from 4 institutions. These rates will vary according to patient population (national databases vs hospital experience) and reporting practices and criteria (active, passive, severity, case definition, and others). The estimated incidence of infectious complications is derived from the Transfusion-Transmissible Infections Monitoring System.

Population, Intervention, Comparator, and Outcomes Questions

We provide recommendations for 2 questions:

1. For hospitalized, hemodynamically stable adult patients, should clinicians transfuse with a restrictive strategy (typical hemoglobin level <7-8 g/dL) vs a liberal strategy (typical hemoglobin level <9-10 g/dL)?
2. For hospitalized, hemodynamically stable pediatric patients (*a*) without congenital heart disease (infancy to 16 years), should clinicians transfuse with a restrictive strategy (hemoglobin level <7-8 g/dL) vs a liberal strategy (hemoglobin level <9-10 g/dL); and (*b*) with congenital heart disease, should clinicians transfuse with a restrictive vs liberal strategy based on the cardiac lesion?

We provide recommendations for patients with acute or prolonged need of transfusions, but not for those who are transfusion dependent (eg, hemoglobinopathies). For adults, we examined subgroups in which the harm and benefit of a particular transfusion threshold might differ from that of overall populations: preexisting coronary artery disease, cardiac surgery, orthopedic surgery, and oncologic or hematologic conditions.

We examined subgroups of children in whom the risk and benefit of transfusion threshold might differ from that of the overall populations of patients: those with heart disease (congenital or acquired) or surgery and hematologic or oncologic conditions. We excluded trials of preterm neonates, which have been reviewed elsewhere.[17]

Values and Preferences

Recommendations are based on the following values and preferences:

- Avoid the adverse effects after RBC transfusion (high value).
- Conserve resources related to RBC transfusions (high value) to ensure blood is available for individuals who need it most.
- Prefer the demonstrated benefits of a restrictive transfusion policy despite the remaining possibility of a small increase in mortality.

Comments and Modification

J.L.C., S.J.S., G.G., S.V., and M.B.P. prepared the draft guideline document that was modified and approved by all panel members and the AABB Clinical Transfusion Medicine Committee. Subsequently, the AABB board of directors and international partner organizations also reviewed the guidelines.

Evidence Review and Grading

Systematic Review

We developed recommendations based on recently published systematic reviews of transfusion thresholds in adults (Cochrane review conducted in 2021)[13] and children (Transfusion and Anemia Expertise Initiative, 2018),[12] supported by literature searches up to February 2021. We reviewed evidence from 45 RCTs with 20 599 adults, 5 RCTs identified within the Transfusion and Anemia Expertise Initiative in 2018, and 2 additional pediatric trials (the 5 RCTs and 2 pediatric trials had a total of 2730 participants).[18-20] The systematic reviews included RCTs in which the transfusion groups were assigned based on a clear transfusion threshold, described as the hemoglobin concentration or hematocrit level required before RBC transfusion. Outcomes in adults included 30-day mortality, nonfatal myocardial infarction, pulmonary edema or congestive heart failure, stroke, thromboembolism, acute kidney injury, infection, hemorrhage, mental confusion, proportion of patients with an allogeneic or autologous RBC transfusion, hemoglobin concentration (postoperative or discharge), number of RBC units transfused, and quality of life. An updated search conducted in January 2023 identified 3 trials with 151 patients.[21-23] For children, outcomes included mortality, thromboembolism, infection, and transfusion requirements.

Analysis

We assessed risk of bias in each RCT as recommended by Cochrane,[24] assessed statistical heterogeneity by both I^2 and χ^2 tests,[25] and used the Instrument to Assess the Credibility of Effect Modification Analyses criteria for making inferences regarding subgroup effects.[26] All analyses were performed with Review Manager version 5.4 (Cochrane Collaboration).[27] Relative risks and the corresponding 95% CIs were calculated for each outcome with random-effects models[28] unless counterintuitive results mandated use of a fixed-effect model. We calculated absolute risks by applying the relative effect to the median of control group risks. When events were anticipated to be rare (eg, for thromboembolism), the Peto odds ratio informed relative effect estimates.

Rating Quality of Evidence and Making Recommendations

We used GRADE methodology to develop these guidelines (see the Supplement).[15,29] The panel came to consensus for quality of evidence ratings that were included in summary of findings tables that served as the bases for panel judgments.[30] In moving from evidence to recommendations, the panel considered criteria in GRADE's evidence to decision framework.[31] The panel came to consensus for all recommendations except for using different restrictive strategy thresholds by clinical subgroup in which a vote was required.

Good Practice Statement

In deciding when a particular patient should undergo transfusion, the panel considers it good clinical practice to consider not only the hemoglobin concentration but also symptoms, signs, other laboratory data, patients' values and preferences, and the overall clinical context. Relevant variables include the rate of hemoglobin level decline, intravascular volume status, dyspnea, decreased exercise tolerance, lightheadedness, chest pain thought to be cardiac in origin, and hypotension or tachycardia unresponsive to fluid challenge. Clinicians should consider alternatives to transfusion, including medical treatment of anemia and blood conservation strategies.

Disclaimer

This practice guideline will not apply to all individual RBC transfusion decisions.

Recommendations for Adults

Recommendation 1

For hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive RBC transfusion strategy in which the transfusion is considered when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence).

Remark: in accordance with the restrictive strategy threshold used in most of the trials for subgroups of patients, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for patients undergoing orthopedic surgery or those with preexisting cardiovascular disease.

Recommendation 2

For hospitalized adult patients, the panel suggests a restrictive RBC transfusion strategy in which transfusion is considered when the hemoglobin concentration is less than 7 g/dL in those with hematologic and oncologic disorders (conditional recommendation, low certainty evidence).

Evidence Summary for Adults

The 45 RCTs with adult participants were conducted across a range of settings, including orthopedic surgery (n = 11), cardiac surgery (n = 8), hematologic and oncologic conditions (n = 7), critical care (n = 8), acute blood loss (n = 6), acute myocardial infarction (n = 3), and vascular surgery (n = 2). The most common liberal transfusion threshold was 9 to 10 g/dL and the most common restrictive threshold was 7 to 8 g/dL.

Table 2 presents the summary of findings comparing restrictive with liberal transfusion strategies for 30-day mortality, multiple morbidities, and transfusion requirements. Thirty trials including data from 16 092 participants evaluated 30-day mortality, with a pooled relative risk of 1.00 (95% CI, 0.86-1.16). The baseline mortality rate was 8.3%, and an absolute difference between transfusion strategies was 0% (95% CI, 1.2% fewer to 1.3% more deaths) (high certainty). The restrictive strategy resulted in a 32.4% absolute reduction (95% CI, 37.3%-27.5% fewer deaths) in receiving a transfusion.

Chance may explain differences in mortality estimates among the clinical conditions (test for subgroup differences, $P = .34$). Given limited trial data in hematologic malignancies (2 trials, N = 149 participants) and an upper CI limit consistent with substantial harm

Table 2. Summary of Findings in Trials Comparing Liberal vs Restrictive Transfusion Strategies on Mortality, Morbidity, and Blood Transfusion in Adults

Outcome, No. of participants (No. of RCTs)	Relative effect (95% CI)	Absolute effects, %			Certainty	Plain language summary
		Restrictive	Liberal	Difference (95% CI)		
30-d Mortality, N = 16 092 (30)	RR, 1.00 (0.86-1.16)	8.3	8.3	0.0 Fewer (1.2 fewer to 1.3 more)	High	Transfusion threshold likely has little or no effect on mortality
MI, N = 14 370 (23)	RR, 1.04 (0.87-1.24)	3.3	3.2	0.1 More (0.4 fewer to 0.8 more)	High	Transfusion threshold has little or no effect on MI
CHF, N = 6610 (15)	RR, 0.86 (0.56-1.33)	3.2	3.7	0.5 Fewer (1.6 fewer to 1.2 more)	Low[a,b]	Transfusion threshold likely has little or no effect on CHF
CVA, N = 13 985 (19)	RR, 0.84 (0.64-1.09)	1.4	1.7	0.3 Fewer (0.6 fewer to 0.2 more)	High	Transfusion threshold likely has little or no effect on CVA
Rebleeding, N = 3412 (8)	RR, 0.80 (0.59-1.09)	12.6	15.8	3.2 Fewer (6.5 fewer to 1.4 to more)	Moderate[a]	Transfusion threshold likely has little or no effect on rebleeding
Infection, N = 16 466 (24)	RR, 0.98 (0.89-1.09)	13.6	13.9	0.3 Fewer (1.5 fewer to 1.2 more)	High	Transfusion threshold likely has little or no effect on infection
Thromboembolism, N = 4201 (13)	OR, 1.11 (0.65-1.88)	1.7	1.5	0.2 More (0.5 fewer to 1.3 more)	Moderate[b]	Transfusion threshold likely has little or no effect on thromboembolism
Delirium, N = 6442 (9)	RR, 1.11 (0.88-1.40)	11.9	10.7	1.2 More (1.3 fewer to 4.3 more)	Moderate[b]	Transfusion threshold likely has little or no effect on delirium
Transfusion, N = 19 419 (41)	RR, 0.60 (0.54-0.66)	48.6	81.0	32.4 Fewer (37.3 to 27.5 fewer)	High	Restrictive transfusion threshold results in large reduction in transfusion

Abbreviations: CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

[a] Downgraded for inconsistency.

[b] Downgraded for imprecision. 95% CIs were calculated with Review Manager version 5.4 (Cochrane).[27] See eFigures 1 through 9 in the Supplement for details.

Table 3. Summary of Findings in Trials of Patients With Hematologic Malignancies and Myocardial Infarction Comparing Liberal vs Restrictive Transfusion Strategies on 30-Day Mortality

Patient group (No. of RCTs)	30-d Mortality relative effect (95% CI)	Absolute effects, %			Certainty
		Restrictive	Liberal	Difference (95% CI)	
Hematologic malignancies, N = 149 (2)	RR, 0.37 (0.07-1.95)	2.4	6.6	4.1 fewer (6.1 fewer to 6.2 more)	Low[a]
Myocardial infarction, N = 820 (3)	RR, 0.99 (0.59-1.65)[b]	6.7	6.8	0.1 fewer (2.8 fewer to 4.4 more)	Low[c,d]

Abbreviations: RCT, randomized controlled trial; RR, relative risk.

[a] Two downgrades for very serious imprecision.

[b] Note that in consultation with a methodologist (GG), a fixed effect model has been presented for this outcome due to low event rate. Random effects model absolute difference = 4.1% more (4.2 fewer and 39.7 more).

[c] Imprecision.

[d] Inconsistency. 95% CIs calculated with Review Manager version 5.4 (Cochrane Collaboration).[27]

(6.2% rate of increased deaths in the restrictive transfusion strategy), certainty of the evidence for mortality in this population was rated low (**Table 3**). Given heterogeneity in results and an upper CI limit consistent with substantial harm (4.4% rate of increased deaths in the restrictive transfusion strategy), the certainty of the evidence was rated low for mortality in acute myocardial infarction (Table 3).

There were no apparent differences between transfusion strategies for the morbidity outcomes (Table 2). Data from 3 RCTs that enrolled 448 participants suggested the risk of bleeding in hematology and oncology patients was uninfluenced by transfusion strategy (relative risk, 1.03; 95% CI, 0.87 to 1.23; absolute difference, 0.6%; 2.7% fewer to 4.8% more bleeding events).[32-34]

The most common restrictive transfusion strategy applied in the trials was 7 or 8 g/dL (**Figure**), although variations included critical care and cardiac surgery trials that used a transfusion strategy of 7 to 7.5 g/dL and orthopedic and acute myocardial infarction trials that used a restrictive strategy of 8 g/dL.[36-64]

Rationale for Recommendations for Adults

The panel recommends that RBC transfusion be administered using a restrictive transfusion strategy of 7 g/dL for most hemodynamically stable adults (strong recommendation, high certainty evidence).

The panel was divided (by vote) on whether to recommend different restrictive transfusion strategy thresholds by clinical subgroup. The rationale for recommending a universal threshold of 7 g/dL is that many trials used this threshold, and there is no strong clinical or biological basis for expecting different effects between 7 and 8 g/dL (with the possible exception of cardiovascular disease and hematology or oncology; see later). Furthermore, the effects on mortality were consistent across all subgroups, and there were no apparent differences in outcomes between trials that used a threshold of 7 and 8 g/dL (see earlier) (Figure). Recommending a hemoglobin threshold of 7 g/dL would conserve more blood.

An alternative view is that the recommendations should closely follow the clinical trial evidence and avoid extrapolating trial results when a threshold of 7 g/dL has not been explicitly tested. Most of the trials in orthopedic surgery used a threshold of 8 g/dL, and the largest trial conducted in cardiac surgery used a threshold of 7.5 g/dL. Some members of the panel thought that higher hemoglobin thresholds might improve outcomes other than mortality, including improved function and recovery after surgery or acute illness.

Figure. Comparison of Randomized Trials in Adults Using Different Restrictive Transfusions for the Outcome of Mortality at 30 Days

Risk of bias
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): objective measures
E Incomplete outcome data (attrition bias)
F Selective reporting (reporting bias)
G Other bias

Study or subgroup	Restrictive threshold		Liberal threshold		Risk ratio (95% CI)	Weight, %	Risk of bias						
	No. of events	Total	No. of events	Total			A	B	C	D	E	F	G
Restrictive, 7.0-7.5 g/dL													
DeZern et al,[33] 2016	1	59	2	30	0.25 (0.02-2.69)	0.4	+	+	+	+	+	+	+
Gillies et al,[36] 2020	2	36	1	26	1.44 (0.14-15.10)	0.4	+	+	+	+	+	+	+
Gobatto et al,[37] 2019	7	23	1	21	6.39 (0.86-47.7)	0.5	+	+	+	+	+	+	?
Parker,[38] 2013	5	100	3	100	1.67 (0.41-6.79)	1.1	+	+	+	+	−	?	+
Hébert et al,[39] 1995	8	33	9	36	0.97 (0.42-2.22)	2.7	+	?	+	+	+	?	+
de Almeida et al,[40] 2015	23	101	8	97	2.76 (1.30-5.87)	3.2	+	+	+	+	+	+	+
Palmieri et al,[41] 2017	16	168	15	177	1.12 (0.57-2.20)	3.8	+	+	+	+	+	+	+
Walsh et al,[42] 2013	12	51	16	49	0.72 (0.38-1.36)	4.1	+	+	+	+	+	+	+
Murphy et al,[43] 2015	26	1000	19	1003	1.37 (0.76-2.46)	4.7	+	+	+	+	+	+	+
Villanueva et al,[44] 2013	19	416	34	417	0.56 (0.32-0.97)	5.2	+	+	+	+	+	?	+
Mazer et al,[45] 2017	74	2427	87	2429	0.85 (0.63-1.15)	9.8	+	+	+	+	+	+	+
Hébert et al,[46] 1999	78	418	98	420	0.80 (0.61-1.04)	10.9	+	+	+	+	+	?	+
Bergamin et al,[47] 2017	84	151	67	149	1.24 (0.99-1.55)	12.0	+	+	+	+	+	+	+
Holst et al,[48] 2014	168	502	175	496	0.95 (0.80-1.13)	13.7	+	+	+	+	+	+	+
Subtotal (95% CI)	5485		5450		1.00 (0.83-1.21)	72.5							
Total events	523		535										
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 26.15$; $df = 13$; $P = .02$; $I^2 = 50\%$													
Test for overall effect: $z = 0.01$; $P = .99$													
Restrictive, <8.0-9.0 g/dL													
Lotke et al,[49] 1999	0	62	0	65	Not estimable		+	?	+	+	+	+	+
Laine et al,[50] 2018	0	40	0	40	Not estimable		?	−	+	+	+	?	+
Grover et al,[51] 2006	0	109	1	109	0.33 (0.01-8.09)	0.2	+	+	+	+	−	?	?
Blair et al,[52] 1986	0	26	2	24	0.19 (0.01-3.67)	0.2	?	?	+	+	+	?	+
Foss et al,[53] 2009	5	60	0	60	11.0 (0.62-194.6)	0.3	+	+	+	+	?	+	+
Carson et al,[54] 1998	1	42	1	42	1.00 (0.06-15.5)	0.3	+	+	+	+	+	?	+
Møller et al,[55] 2019	1	29	1	29	1.00 (0.07-15.2)	0.3	+	+	+	+	+	+	?
Webert et al,[56] 2008	1	29	2	31	0.53 (0.05-5.58)	0.4	+	+	+	+	+	?	+
Cooper et al,[57] 2011	2	23	1	21	1.83 (0.18-18.7)	0.4	+	+	+	+	+	+	+
Carson et al,[58] 2013	7	55	1	55	7.00 (0.89-55.0)	0.5	+	+	+	+	+	+	+
Bush et al,[59] 1997	4	50	4	49	0.98 (0.26-3.70)	1.2	+	+	+	+	+	?	+
Hajjar et al,[60] 2010	15	249	13	253	1.17 (0.57-2.41)	3.5	+	+	+	+	+	+	+
Gregersen et al,[61] 2015	21	144	12	140	1.70 (0.87-3.32)	3.8	+	+	+	+	+	+	+
Jairath et al,[62] 2015	14	257	25	382	0.83 (0.44-1.57)	4.1	+	−	+	+	+	?	+
Ducrocq et al,[63] 2021	19	342	25	324	0.72 (0.40-1.28)	4.8	+	+	+	+	+	+	+
Carson et al,[64] 2011	43	1009	52	1007	0.83 (0.56-1.22)	7.7	+	+	+	+	+	+	+
Subtotal (95% CI)	2526		2631		0.97 (0.75-1.24)	27.5							
Total events	133		140			100							
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 13.35$; $df = 13$; $P = .42$; $I^2 = 3\%$													
Test for overall effect: $z = 0.27$; $P = .78$													
Total (95% CI)	8011		8081		0.99 (0.86-1.15)								
Total events	656		675										
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 39.41$; $df = 27$; $P = .06$; $I^2 = 31\%$													
Test for overall effect: $z = 0.09$; $P = .93$													
Test for subgroup differences: $\chi^2 = 0.05$; $df = 21$; $P = .82$; $I^2 = 0\%$													

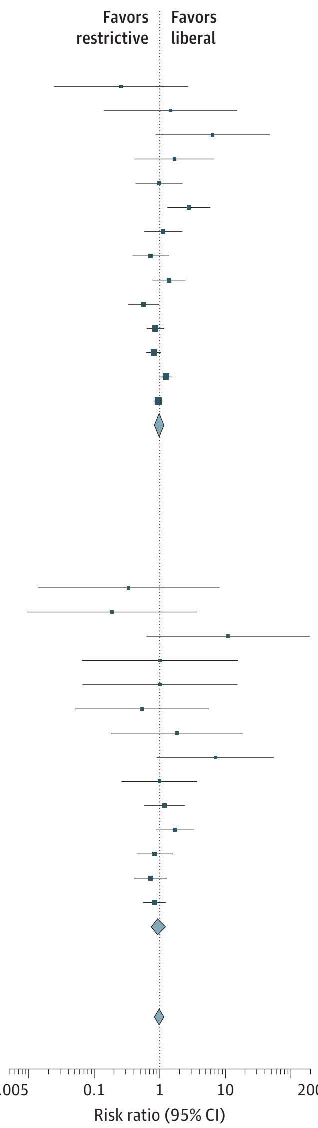

Figure modified from the Cochrane review[13] by removing 1 trial performed with pediatric patients (Lacroix et al[35]) and placing a second trial (Laine et al[36]) in the correct subgroup. Relative risks and the corresponding 95% CIs were calculated for each outcome with random-effects models unless counterintuitive results mandated use of a fixed-effect model. The blue pluses indicate low risk of bias; gray question marks, unclear risk of bias; and orange minuses, high risk of bias.

For patients with acute and chronic ischemic cardiac disease, there remains substantial uncertainty regarding the safety of restrictive thresholds. As in the AABB's previous guidelines,[10,11] the panel chose not to recommend for or against a liberal or restrictive transfusion threshold for patients with acute myocardial infarction. Although the pooled estimates of effects on mortality with acute myocardial infarction were almost identical to the overall effects, the absolute and relative risk estimates were imprecise, with wide CIs. The panel noted that the MINT trial (including 3500 participants with acute myocardial infarction) is nearing completion. MINT compares a liberal transfusion at 10 g/dL with a restrictive transfusion strategy of 7 to 8 g/dL.[65]

In the setting of hematology and oncology inpatients, the panel suggests transfusion at 7 g/dL (conditional, low certainty evidence).

Table 4. Summary of Findings in Trials Comparing Liberal vs Restrictive Transfusion Strategies on Mortality, Morbidity, and Blood Transfusion in Children

Outcome, No. of participants (No. of RCTs)	Relative effect (95% CI)	Anticipated absolute effects (95% CI), %			Certainty	Plain language summary
		Restrictive	Liberal	Difference (95% CI)		
Participants exposed to blood transfusion, 799 (2)	RR, 0.51 (0.41-0.65)	48.0	94.2	46.2 Fewer (55.6 to 33 fewer)	High	Restrictive transfusion threshold has a large effect on reduction of transfusion
30-d Mortality (follow-up range, 28-30 d), 972 (5)	RR, 0.44 (0.04-4.45)	1.7	3.9	2.2 Fewer (3.8 fewer to 13.5 more)	Moderate[a,b]	Transfusion threshold likely has little effect on mortality
Pneumonia, 744 (2)	RR, 1.14 (0.58-2.23)	4.6	4.0	0.6 More (1.7 fewer to 5 more)	Moderate[a]	Transfusion threshold likely has little or no effect on pneumonia
Thrombosis (follow-up, 28 d), 799 (2)	OR, 1.78 (0.61-5.22)	2.3	1.3	1.0 More (0.5 fewer to 5.4 more)	Low[c]	Transfusion threshold may have little or no effect on thrombosis
30-d Mortality subgroup analysis by clinical specialties (cardiac surgery), 454 (4)	RR, 0.62 (0.12-3.13)	1.1	1.8	0.7 Fewer (1.6 to 3.8 more)	Low[a,b,d]	Transfusion threshold may have little effect on mortality

Abbreviations: OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

[a] One downgrade for imprecision; even the largest included study was not adequately powered for the outcome of mortality. Smaller studies were not always informative because they included low-risk populations only, terminated early, or reported no or few events.

[b] For 1 study reporting mortality data only within the scope of its study period, we obtained supplementary data for 30 days.

[c] Two downgrades for serious imprecision (rare event).

[d] Downgraded for imprecision. 95% CIs were calculated with Review Manager version 5.4 (Cochrane Collaboration).[27] See eFigures 10 through 14 in the Supplement for details.

Although the number of patients enrolled in these trials was smaller than that in many other clinical subgroups, because new RCTs have suggested neither harm nor increased bleeding when using a restrictive threshold, this recommendation differs from the 2016 guidelines.[11] There were insufficient trial data to inform recommendations in outpatient transfusion management.

Recommendations for Children

Recommendation 3

For critically ill children and hospitalized children at risk of critical illness who are hemodynamically stable and without a transfusion-dependent hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, the international panel recommends a restrictive transfusion strategy in which a transfusion is considered when the hemoglobin level is less than 7 g/dL compared with one of less than 9.5 g/dL (strong recommendation, moderate certainty evidence).

Recommendation 4

The international panel suggests considering a transfusion threshold for hemodynamically stable children with congenital heart disease that is based on the cardiac abnormality and stage of surgical repair: 7 g/dL (biventricular repair), 9 g/dL (single-ventricle palliation), or 7 to 9 g/dL (uncorrected congenital heart disease) (conditional recommendation, low certainty evidence).

Evidence Summary for Children

The populations of children included in the RCTs were critically ill patients (n = 2),[20,35] those with hematologic conditions (n = 1),[66] those with acquired and congenital heart disease (n = 3),[67-69] and those with severe (malarial) anemia (n = 1)[18,19] (Table 4). The largest single intensive care unit RCT reported a 51.8% absolute reduction in transfusions in the restrictive strategy group compared with the liberal strategy group,[35] with no significant difference reported for 30-day mortality within a meta-analysis of 5 RCTs (relative risk, 0.44; 95% CI, 0.04-4.45). In the latter analysis, the baseline mortality rate was 3.9%, with an absolute difference of 1.7% (95% CI, 0.2% fewer to 17.5% more deaths) (moderate certainty). There were no clear differences in the morbidity outcomes (Table 4). We evaluated the transfusion strategies on 30-day mortality in subgroups of heart disease (acquired and congenital) (eFigure 12 in the Supplement). Chance may explain differences in mortality among the clinical populations. The certainty of the evidence was rated as low because of small sample size and various surgical settings and clinical conditions.

Rationale for Recommendations for Children

It is likely that mortality is similar for restrictive strategies compared with liberal ones (moderate certainty, rated down because of inconsistency and the remaining possibility of an increase in 30-day mortality after application of a restrictive strategy of up to 3%).

Although the direct evidence was dominated by a single trial,[35] a large well-conducted RCT of transfusion volumes and timing in anemic children (hemoglobin level <6 g/dL) with malaria also supported the safety of a restrictive transfusion threshold. The panel concluded this evidence supported a strong recommendation.[18,19]

Children with acquired or congenital heart disease form a subgroup in which there remains uncertainty regarding the pathophysiologic safety of restrictive thresholds, and the RCTs had recruited different populations of children undergoing surgery.

Discussion

The expanding number of RCTs of RBC transfusion thresholds informs best practice in adults and children. Many of the RCTs tested different protocols including thresholds for RBC transfusion that varied by clinical setting. The panel debated whether to recommend a threshold of 7 g/dL for all hemodynamically stable adults or adopt a higher threshold in select clinical subgroups (cardiac surgery, 7.5 g/dL; orthopedic surgery and chronic

Box. Red Blood Cell Transfusion Guidelines Since 2016

Society and Recommendation

UK National Clinical Guidelines Centre (2016)[79]
Restrictive threshold (7 g/dL) for patients who do not have major hemorrhage or acute coronary syndrome or need long-term transfusion. In acute coronary syndrome, transfusion should be considered at a threshold of 8 g/dL. Clinicians should consider setting individual targets for patients with chronic anemia.

European Society of Anaesthesiology (2017)[80]
Target hemoglobin level of 7-9 g/dL in patients with active bleeding

Frankfurt Germany Consensus conference (2018)[81]
Varied depending on clinical setting: 7 g/dL for critically ill patients, 7.5 g/dL in cardiac surgery, 8 g/dL in hip fracture and cardiovascular disease, and 7-8 g/dL in acute gastrointestinal bleeding

Pediatric Critical Care Transfusion and Anemia Expertise Initiative (2018)[12]
Varied depending on clinical setting: 7 g/dL for hemodynamically stable critically ill children; for hemodynamically stable children with congenital heart disease, varied based on cardiac abnormality and stage of repair; 7 g/dL biventricular repair, 9 g/dL stage 1 and stage 2 palliation

Society of Cardiovascular Anesthesiologists (2019)[82]
Transfusion threshold of 7.5 g/dL is reasonable in cardiac surgery

The Society of Thoracic Surgeons and affiliated groups (2021)[83]
Restrictive transfusion strategy, although a specific hemoglobin level was not provided

cardiovascular disease, 8 g/dL), ultimately concluding that each approach has its merits. Our guideline also now incorporates specific guidance for hemodynamically stable children, and the findings support recommendations for a restrictive strategy (threshold <7 g/dL for children, excluding those with congenital heart disease). Minimizing unnecessary complications of transfusion and responding to the ongoing global challenges of having a safe and secure blood supply will require effective strategies, including blood management programs, for implementation of these guidelines.

Good transfusion practice should rely not only on hemoglobin concentration thresholds but also incorporation of patients' symptoms, signs, comorbid conditions, rate of bleeding, values, and preferences. This guidance is particularly important because clinicians commonly use only hemoglobin concentration to decide when to transfuse.[70] Blood management programs that audit blood should attend to these broader considerations in their policies and decisions. Given that RCTs demonstrated no effect on mortality,[71,72] the storage age of transfused RBCs need not be considered in transfusion decisions.

Similar to older guidelines,[73-78] this guideline and other guidelines published after 2016 continue to recommend restrictive transfusion strategies[79-83] (**Box**).

Research Recommendations

Ongoing trials for patients with acute myocardial infarction, vascular disease, and neurologic disorders will inform transfusion practice.[17] Further analyses of subgroups of trials using individual patient data from existing trials are needed by age, sex, preexisting cardiovascular disease, pregnancy status, and other clinical factors. There are gaps in the evidence regarding the needs of individuals with myelodysplastic syndromes who are transfusion dependent. To modify symptoms of anemia, such people may require higher thresholds for transfusions. Given the findings indicating the safety of restrictive thresholds, new trial designs should focus on the safety of lower transfusion thresholds (eg, 5-6 g/dL), incorporation of physiologic parameters, and the conduct of health economic analyses.

Conclusion

Our panel recommends restrictive transfusion strategies, typically with a threshold of 7 g/dL for both adult and pediatric patients. The panel recognizes important additional considerations, including signs, symptoms, comorbid conditions, and patient values and preferences, that will differ between patients. The recommendation is strong, based on moderate certainty evidence for most patients, but conditional, based on lower certainty evidence subgroups that include hematologic and oncologic disorders in adults and cyanotic cardiac condition in infants.

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Supplemental Online Content

Carson JL, Stanworth SJ, Guyatt G, et al.. Red blood cell transfusion: 2023 AABB international guidelines. *JAMA*.
doi:10.1001/jama.2023.12914

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

eAppendix. Overview of Methods and Clarification of Grade Methodology

All meta-analyses undertaken in the course of the original Cochrane review referenced within the main paper (Carson et al 2021) were conducted using RevMan 5.4 (RevMan 5.4 2020). All statistical methods and the assumptions underlying them can be found in an open access document (Deeks 2010) as well as within the Cochrane Handbook itself (Higgins et al 2011).

Certain results of meta-analysis presented within the present paper differ from Carson et al 2021 for two reasons. First, we decided to conduct separate analyses for outcomes related to children, and therefore removed the study by Lacroix and colleagues (Lacroix 2007) which currently is included within all primary analyses within the latest published update of the Cochrane review. Secondly, we corrected data for a small study (Laine 2018). Finally, we conducted subgroup analyses of mortality for haematological malignancies as well as a subgroup for acute myocardial infarction using a fixed effects model, following advice from a methodologist. These were not shown in the Cochrane review but are based on data found there.

The Summary of Findings tables presented in the main paper were developed using GRADEPro software (GRADEPro GDT 2022) and in accordance with published guidance (Guyatt et al 2013; Schünemann et al 2013). The first table (including data for adult trial participants) closely resembles the conclusions which appear in the Cochrane review. The second Summary of Findings table (relating only to children) was developed as part of an ongoing update of the Cochrane review, and was finalised as part of the AABB guidelines process.

Below, we present figures which relate to each row (outcome) of the Summary of Findings tables for adults and for children, together with a graphical presentation of the individual ratings we gave each trial for risk of bias for the domains listed in the legend provided. It will be noted that 'high risk of bias' was not given as an assessment for categories relating to blinding, as blinding was often unfeasible, if not impossible. We decided that with the exception of outcomes related to function and quality of life (not dealt with in this paper) this aspect of trial conduct did not constitute a serious risk of bias.

It should be noted when considering the domain of 'risk of bias' as part of GRADE (on an outcome by outcome, and not a study by study basis), no outcome within the tables presented for adults or children was downgraded for overall risk of bias. Downgrading(s), when we felt obliged to make them, were either for the domain of inconsistency (Guyatt et al 2011a) or for imprecision (Guyatt et al 2011b). Interested readers may also find it useful to examine the forest plots below with the Summary of Findings tables.

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Forest plots for 30-day mortality and morbidity outcomes in adults

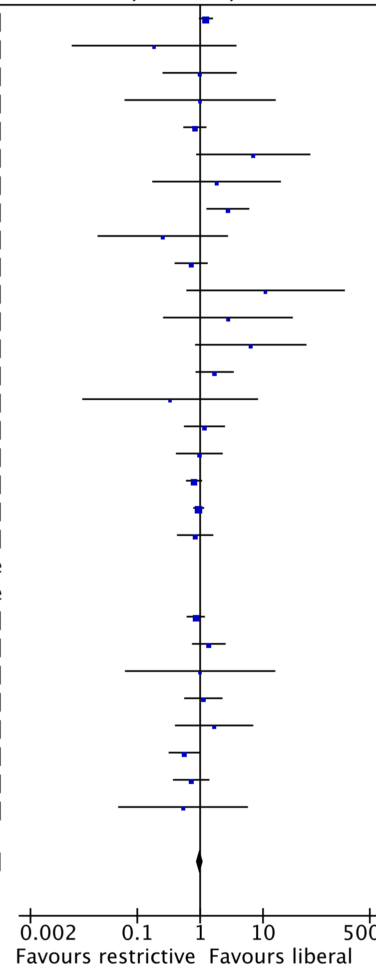
eFigure 1: Mortality at 30 days

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
Bergamin 2017	84	151	67	149	11.9%	1.24 [0.99, 1.55]	+	+	+	+	+	+	+
Blair 1986	0	26	2	24	0.3%	0.19 [0.01, 3.67]	?	?	+	+	+	?	+
Bush 1997	4	50	4	49	1.2%	0.98 [0.26, 3.70]	+	+	+	+	+	?	+
Carson 1998	1	42	1	42	0.3%	1.00 [0.06, 15.47]	+	+	+	+	+	?	+
Carson 2011	43	1009	52	1007	7.7%	0.83 [0.56, 1.22]	+	+	+	+	+	+	+
Carson 2013	7	55	1	55	0.5%	7.00 [0.89, 55.01]	+	+	+	+	+	+	+
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18, 18.70]	+	+	+	+	+	+	+
de Almeida 2015	23	101	8	97	3.2%	2.76 [1.30, 5.87]	+	+	+	+	+	+	+
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02, 2.69]	+	+	+	+	+	+	+
Ducrocq 2021	19	342	25	324	4.8%	0.72 [0.40, 1.28]	+	+	+	+	+	+	+
Foss 2009	5	60	0	60	0.3%	11.00 [0.62, 194.63]	+	+	+	+	?	+	+
Gillies 2020	2	26	1	36	0.4%	2.77 [0.26, 28.95]	+	+	+	+	+	+	+
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86, 47.70]	+	+	+	+	+	+	?
Gregersen 2015	21	144	12	140	3.9%	1.70 [0.87, 3.32]	+	+	+	+	+	+	+
Grover 2006	0	109	1	109	0.2%	0.33 [0.01, 8.09]	+	+	+	+	−	?	?
Hajjar 2010	15	249	13	253	3.4%	1.17 [0.57, 2.41]	+	+	+	+	+	+	+
Hébert 1995	8	33	9	36	2.8%	0.97 [0.42, 2.22]	+	?	+	+	+	?	+
Hébert 1999	78	418	98	420	10.8%	0.80 [0.61, 1.04]	+	+	+	+	+	?	+
Holst 2014	168	502	175	496	13.5%	0.95 [0.80, 1.13]	+	+	+	+	+	+	+
Jairath 2015	14	257	25	382	4.2%	0.83 [0.44, 1.57]	+	−	+	+	+	?	+
Laine 2018	0	40	0	40		Not estimable	?	−	+	+	+	?	+
Lotke 1999	0	62	0	65		Not estimable	+	?	+	+	+	+	+
Mazer 2017	74	2427	87	2429	9.8%	0.85 [0.63, 1.15]	+	+	+	+	+	+	+
Murphy 2015	26	1000	19	1003	4.7%	1.37 [0.76, 2.46]	+	+	+	+	+	+	+
Møller 2019	1	29	1	29	0.3%	1.00 [0.07, 15.24]	+	+	+	+	+	+	?
Palmieri 2017	16	168	15	177	3.8%	1.12 [0.57, 2.20]	+	+	+	+	+	+	+
Parker 2013	5	100	3	100	1.1%	1.67 [0.41, 6.79]	+	+	+	+	−	?	+
Villanueva 2013	19	416	34	417	5.2%	0.56 [0.32, 0.97]	+	+	+	+	+	?	+
Walsh 2013	12	51	16	49	4.2%	0.72 [0.38, 1.36]	+	+	+	+	+	+	+
Webert 2008	1	29	2	31	0.4%	0.53 [0.05, 5.58]	+	+	+	+	+	?	+
Total (95% CI)		**8001**		**8091**	**100.0%**	**1.00 [0.86, 1.16]**							
Total events	656		675										

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 40.06$, df = 27 (P = 0.05); $I^2 = 33\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Risk Ratio M-H, Random, 95% CI



Risk of bias legend

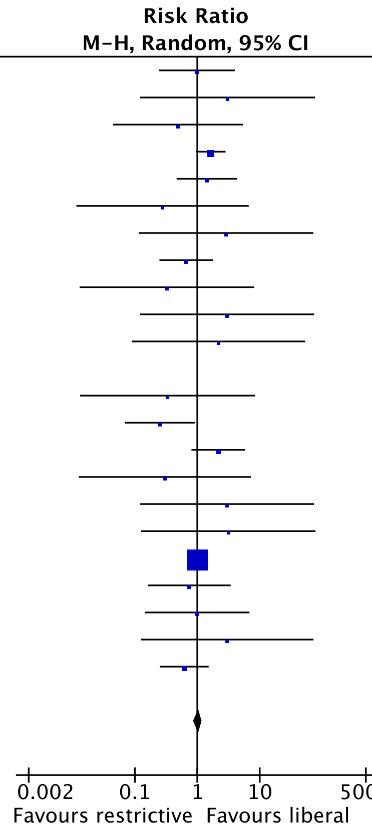
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective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

eFigure 2: Myocardial infarction

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
Bergamin 2017	4	151	4	149	1.7%	0.99 [0.25, 3.87]	+	+	+	+	+	+	+
Bracey 1999	1	212	0	216	0.3%	3.06 [0.13, 74.61]	-	-	+	+	+	?	+
Bush 1997	1	50	2	49	0.6%	0.49 [0.05, 5.23]	+	+	+	+	+	?	+
Carson 2011	38	1009	23	1007	12.3%	1.65 [0.99, 2.75]	+	+	+	+	+	+	+
Carson 2013	7	54	5	55	2.7%	1.43 [0.48, 4.22]	+	+	+	+	+	+	+
Cooper 2011	0	23	1	19	0.3%	0.28 [0.01, 6.45]	+	+	+	+	+	+	+
de Almeida 2015	1	101	0	97	0.3%	2.88 [0.12, 69.91]	+	+	+	+	+	+	+
Ducrocq 2021	7	342	10	324	3.5%	0.66 [0.26, 1.72]	+	+	+	+	+	+	+
Fan 2014	0	94	1	92	0.3%	0.33 [0.01, 7.91]	+	+	+	+	+	+	+
Foss 2009	1	60	0	60	0.3%	3.00 [0.12, 72.20]	+	+	+	+	?	+	+
Gillies 2020	1	36	0	26	0.3%	2.19 [0.09, 51.70]	+	+	+	+	+	+	+
Gobatto 2019	0	23	0	21		Not estimable	+	+	+	+	+	+	?
Grover 2006	0	109	1	109	0.3%	0.33 [0.01, 8.09]	+	+	+	+	-	?	?
Hébert 1999	3	418	12	420	2.0%	0.25 [0.07, 0.88]	+	+	+	+	+	?	+
Holst 2014	13	488	6	489	3.5%	2.17 [0.83, 5.67]	+	+	+	+	+	+	+
Johnson 1992	0	20	1	18	0.3%	0.30 [0.01, 6.97]	-	?	+	+	+	?	+
Laine 2018	1	40	0	40	0.3%	3.00 [0.13, 71.51]	?	-	+	+	+	?	+
Lotke 1999	1	62	0	65	0.3%	3.14 [0.13, 75.72]	+	?	+	+	+	+	+
Mazer 2017	144	2428	144	2429	63.7%	1.00 [0.80, 1.25]	+	+	+	+	+	+	+
Murphy 2015	3	987	4	981	1.4%	0.75 [0.17, 3.32]	+	+	+	+	+	+	+
Møller 2019	2	29	2	29	0.9%	1.00 [0.15, 6.63]	+	+	+	+	+	+	?
Shehata 2012	1	25	0	25	0.3%	3.00 [0.13, 70.30]	+	+	+	+	+	+	+
Villanueva 2013	8	444	13	445	4.2%	0.62 [0.26, 1.47]	+	+	+	+	+	?	+
Total (95% CI)		**7205**		**7165**	**100.0%**	**1.04 [0.87, 1.24]**							
Total events	237		229										

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 18.63$, df = 21 (P = 0.61); $I^2 = 0\%$

Test for overall effect: Z = 0.39 (P = 0.70)



Risk of bias legend

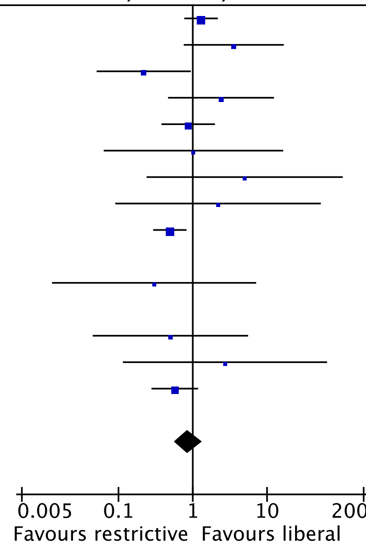
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective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

eFigure 3: Congestive heart failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
Carson 2011	35	1009	27	1007	19.6%	1.29 [0.79, 2.12]	+	+	+	+	+	+	+
Carson 2013	7	54	2	55	6.2%	3.56 [0.78, 16.40]	+	+	+	+	+	+	+
Cooper 2011	2	24	8	21	6.8%	0.22 [0.05, 0.92]	+	+	+	+	+	+	+
de Almeida 2015	5	101	2	97	5.7%	2.40 [0.48, 12.08]	+	+	+	+	+	+	+
Ducrocq 2021	11	342	12	324	13.8%	0.87 [0.39, 1.94]	+	+	+	+	+	+	+
Fan 2014	1	94	1	96	2.3%	1.02 [0.06, 16.09]	+	+	+	+	+	+	+
Foss 2009	2	60	0	60	1.9%	5.00 [0.25, 102.00]	+	+	+	+	?	+	+
Gillies 2020	1	36	0	26	1.8%	2.19 [0.09, 51.70]	+	+	+	+	+	+	+
Hébert 1999	22	418	45	420	19.6%	0.49 [0.30, 0.80]	+	+	+	+	+	?	+
Holst 2014	0	488	0	489		Not estimable	+	+	+	+	+	+	+
Johnson 1992	0	20	1	18	1.8%	0.30 [0.01, 6.97]	−	?	+	+	+	?	+
Kola 2020	0	112	0	112		Not estimable	+	+	+	+	+	?	+
Parker 2013	1	100	2	100	3.0%	0.50 [0.05, 5.43]	+	+	+	+	−	?	+
Stanworth 2020	1	20	0	18	1.8%	2.71 [0.12, 62.70]	+	+	+	+	+	+	+
Villanueva 2013	12	444	21	445	15.7%	0.57 [0.29, 1.15]	+	+	+	+	+	?	+
Total (95% CI)		**3322**		**3288**	**100.0%**	**0.86 [0.56, 1.33]**							
Total events	100		121										

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 19.88$, df = 12 (P = 0.07); $I^2 = 40\%$
Test for overall effect: Z = 0.67 (P = 0.50)

Risk Ratio
M-H, Random, 95% CI



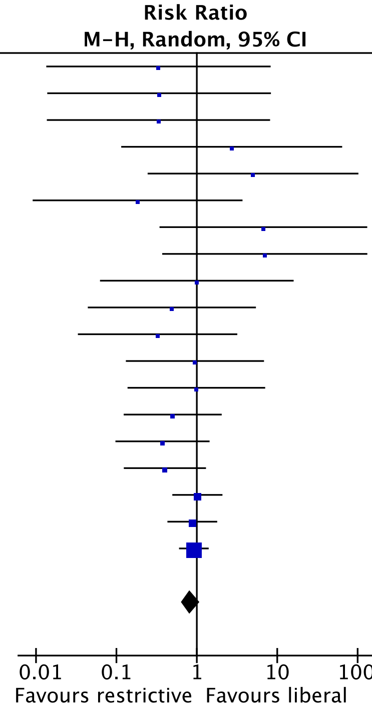
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition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

eFigure 4: Cerebrovascular accident

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
Parker 2013	0	100	1	100	0.7%	0.33 [0.01, 8.09]	+	+	+	+	−	?	+
Carson 2013	0	54	1	55	0.7%	0.34 [0.01, 8.15]	+	+	+	+	+	+	+
Carson 1998	0	42	1	42	0.7%	0.33 [0.01, 7.96]	+	+	+	+	+	?	+
Johnson 1992	1	20	0	18	0.7%	2.71 [0.12, 62.70]	−	?	+	+	+	?	+
Møller 2019	2	29	0	29	0.8%	5.00 [0.25, 99.82]	+	+	+	+	+	+	?
Gobatto 2019	0	23	2	21	0.8%	0.18 [0.01, 3.61]	+	+	+	+	+	+	?
de Almeida 2015	3	101	0	97	0.8%	6.73 [0.35, 128.52]	+	+	+	+	+	+	+
Shehata 2012	3	25	0	25	0.8%	7.00 [0.38, 128.87]	+	+	+	+	+	+	+
Foss 2009	1	60	1	60	0.9%	1.00 [0.06, 15.62]	+	+	+	+	?	+	+
Fan 2014	1	94	2	92	1.2%	0.49 [0.05, 5.30]	+	+	+	+	+	+	+
Koch 2017	1	363	3	354	1.4%	0.33 [0.03, 3.11]	+	?	+	+	+	?	+
Ducrocq 2021	2	342	2	324	1.9%	0.95 [0.13, 6.69]	+	+	+	+	+	+	+
Bergamin 2017	2	151	2	149	1.9%	0.99 [0.14, 6.91]	+	+	+	+	+	+	+
Villanueva 2013	3	444	6	445	3.7%	0.50 [0.13, 1.99]	+	+	+	+	+	?	+
Carson 2011	3	1009	8	1007	4.0%	0.37 [0.10, 1.41]	+	+	+	+	+	+	+
Holst 2014	4	488	10	489	5.3%	0.40 [0.13, 1.27]	+	+	+	+	+	+	+
Hajjar 2010	15	249	15	253	14.7%	1.02 [0.51, 2.03]	+	+	+	+	+	+	+
Murphy 2015	15	989	17	985	14.9%	0.88 [0.44, 1.75]	+	+	+	+	+	+	+
Mazer 2017	45	2428	49	2429	44.0%	0.92 [0.62, 1.37]	+	+	+	+	+	+	+
Total (95% CI)		**7011**		**6974**	**100.0%**	**0.84 [0.64, 1.09]**							
Total events	101		120										

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.80$, df = 18 (P = 0.80); $I^2 = 0\%$

Test for overall effect: Z = 1.32 (P = 0.19)



Risk of bias legend

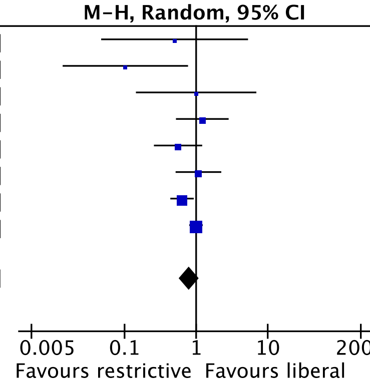
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective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

eFigure 5: Rebleeding

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
Shehata 2012	1	25	2	25	1.6%	0.50 [0.05, 5.17]	+	+	+	+	+	+	+
Blair 1986	1	26	9	24	2.2%	0.10 [0.01, 0.75]	?	?	+	+	+	?	+
Laine 2018	2	40	2	40	2.4%	1.00 [0.15, 6.76]	?	–	+	+	+	?	+
Hajjar 2010	12	249	10	253	10.2%	1.22 [0.54, 2.77]	+	+	+	+	+	+	+
Jairath 2015	9	257	24	383	11.6%	0.56 [0.26, 1.18]	+	–	+	+	+	?	+
Kola 2020	14	112	13	112	12.6%	1.08 [0.53, 2.19]	+	+	+	+	+	?	+
Villanueva 2013	45	444	71	445	25.7%	0.64 [0.45, 0.90]	+	+	+	+	+	?	+
Holst 2014	147	488	148	489	33.6%	1.00 [0.82, 1.20]	+	+	+	+	+	+	+
Total (95% CI)		**1641**		**1771**	**100.0%**	**0.80 [0.59, 1.09]**							
Total events	231		279										

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 12.24$, df = 7 (P = 0.09); $I^2 = 43\%$
Test for overall effect: Z = 1.40 (P = 0.16)

Risk Ratio
M-H, Random, 95% CI



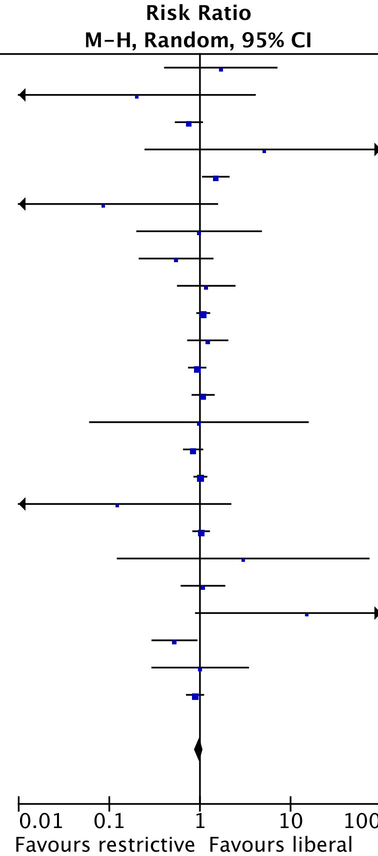
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition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

eFigure 6: Infection

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F
Bracey 1999	5	212	3	216	0.5%	1.70 [0.41, 7.02]	-	-	+	+	?	+
Carson 1998	0	42	2	42	0.1%	0.20 [0.01, 4.04]	+	+	+	+	?	+
Carson 2011	56	1009	74	1007	6.0%	0.76 [0.54, 1.06]	+	+	+	+	+	+
Carson 2013	2	54	0	55	0.1%	5.09 [0.25, 103.64]	+	+	+	+	+	+
de Almeida 2015	53	101	34	97	6.2%	1.50 [1.08, 2.08]	+	+	+	+	+	+
Ducrocq 2021	0	342	5	324	0.1%	0.09 [0.00, 1.55]	+	+	+	+	+	+
Fan 2014	3	94	3	92	0.4%	0.98 [0.20, 4.72]	+	+	+	+	+	+
Foss 2009	6	60	11	60	1.1%	0.55 [0.22, 1.38]	+	+	+	?	+	+
Gillies 2020	13	36	8	26	1.8%	1.17 [0.57, 2.42]	+	+	+	+	+	+
Gregersen 2015	104	144	93	140	12.8%	1.09 [0.93, 1.27]	+	+	+	+	+	+
Hajjar 2010	30	249	25	253	3.3%	1.22 [0.74, 2.01]	+	+	+	+	+	+
Hébert 1999	117	418	126	420	10.1%	0.93 [0.75, 1.15]	+	+	+	+	?	+
Jairath 2015	67	257	92	383	7.8%	1.09 [0.83, 1.42]	+	-	+	+	?	+
Koch 2017	1	363	1	354	0.1%	0.98 [0.06, 15.53]	+	?	+	+	?	+
Mazer 2017	121	2428	144	2429	9.2%	0.84 [0.66, 1.06]	+	+	+	+	+	+
Murphy 2015	238	936	240	954	12.8%	1.01 [0.87, 1.18]	+	+	+	+	+	+
Nielsen 2014	0	30	4	33	0.1%	0.12 [0.01, 2.17]	+	+	+	+	+	?
Palmieri 2017	89	168	91	177	10.6%	1.03 [0.84, 1.26]	+	+	+	+	+	+
Parker 2013	1	100	0	100	0.1%	3.00 [0.12, 72.77]	+	+	+	-	?	+
Prick 2014	24	211	22	209	2.9%	1.08 [0.63, 1.87]	+	+	+	-	+	+
Shehata 2012	7	25	0	25	0.1%	15.00 [0.90, 249.30]	+	+	+	+	+	+
So-Osman 2013	17	299	33	304	2.7%	0.52 [0.30, 0.92]	+	+	+	+	?	+
Tay 2020	5	149	5	150	0.7%	1.01 [0.30, 3.41]	+	+	+	+	+	+
Villanueva 2013	119	444	135	445	10.3%	0.88 [0.72, 1.09]	+	+	+	+	?	+
Total (95% CI)		**8171**		**8295**	**100.0%**	**0.98 [0.89, 1.09]**						
Total events	1078		1151									

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 33.63$, df = 23 (P = 0.07); $I^2 = 32\%$

Test for overall effect: Z = 0.33 (P = 0.74)



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Incomplete outcome data (attrition bias)

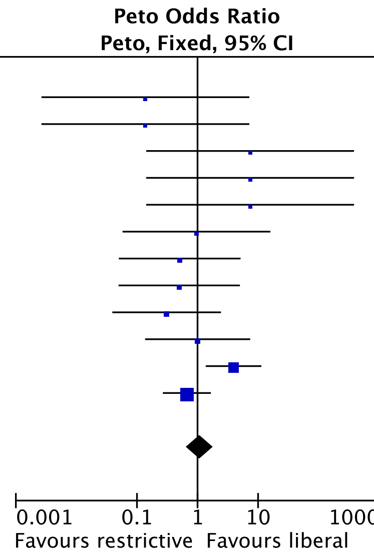
(**E**) Selective reporting (reporting bias)

(**F**) Other bias

eFigure 7: Thromboembolism

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	A	B	C	D	E	F	G
Laine 2018	0	40	0	40		Not estimable	?	-	+	+	+	?	+
Carson 2013	0	54	1	55	1.8%	0.14 [0.00, 6.95]	+	+	+	+	+	+	+
So-Osman 2013	0	299	1	304	1.8%	0.14 [0.00, 6.93]	+	+	+	+	+	?	+
Shehata 2012	1	25	0	25	1.8%	7.39 [0.15, 372.38]	+	+	+	+	+	+	+
Carson 1998	1	42	0	42	1.8%	7.39 [0.15, 372.38]	+	+	+	+	+	?	+
Parker 2013	1	100	0	100	1.8%	7.39 [0.15, 372.38]	+	+	+	+	-	?	+
de Almeida 2015	1	101	1	97	3.6%	0.96 [0.06, 15.47]	+	+	+	+	+	+	+
Foss 2009	1	60	2	60	5.4%	0.51 [0.05, 4.97]	+	+	+	+	?	+	+
Fan 2014	1	94	2	92	5.4%	0.50 [0.05, 4.85]	+	+	+	+	+	+	+
Gobatto 2019	1	23	3	21	6.8%	0.31 [0.04, 2.36]	+	+	+	+	+	+	?
Prick 2014	2	226	2	227	7.2%	1.00 [0.14, 7.18]	+	+	+	+	-	+	+
Møller 2019	18	29	8	29	26.5%	3.94 [1.41, 10.98]	+	+	+	+	+	+	?
Carson 2011	8	1009	12	1007	36.0%	0.67 [0.28, 1.61]	+	+	+	+	+	+	+
Total (95% CI)		**2102**		**2099**	**100.0%**	**1.11 [0.65, 1.88]**							
Total events	35		32										

Heterogeneity: $Chi^2 = 14.48$, df = 11 (P = 0.21); $I^2 = 24\%$
Test for overall effect: Z = 0.37 (P = 0.71)



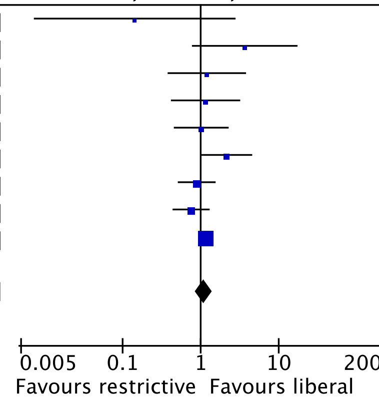
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition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

eFigure 8: Delirium

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
Parker 2013	0	100	3	100	0.6%	0.14 [0.01, 2.73]	+	+	+	+	-	?	+
Lotke 1999	7	62	2	65	2.2%	3.67 [0.79, 16.99]	+	?	+	+	+	+	+
Foss 2009	6	60	5	60	4.0%	1.20 [0.39, 3.72]	+	+	+	+	?	+	+
Gillies 2020	8	36	5	26	5.0%	1.16 [0.43, 3.13]	+	+	+	+	+	+	+
So-Osman 2013	12	299	12	304	7.6%	1.02 [0.46, 2.23]	+	+	+	+	+	?	+
Gregersen 2015	19	89	9	90	8.5%	2.13 [1.02, 4.46]	+	+	+	+	+	+	+
Fan 2014	20	94	22	92	14.2%	0.89 [0.52, 1.52]	+	+	+	+	+	+	+
Carson 2011	16	53	22	55	14.6%	0.75 [0.45, 1.27]	+	+	+	+	+	+	+
Mazer 2017	306	2428	264	2429	43.2%	1.16 [0.99, 1.35]	+	+	+	+	+	+	+
Total (95% CI)		**3221**		**3221**	**100.0%**	**1.11 [0.88, 1.40]**							
Total events	394		344										

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.29$, df = 8 (P = 0.24); $I^2 = 22\%$
Test for overall effect: Z = 0.87 (P = 0.39)

Risk Ratio
M-H, Random, 95% CI



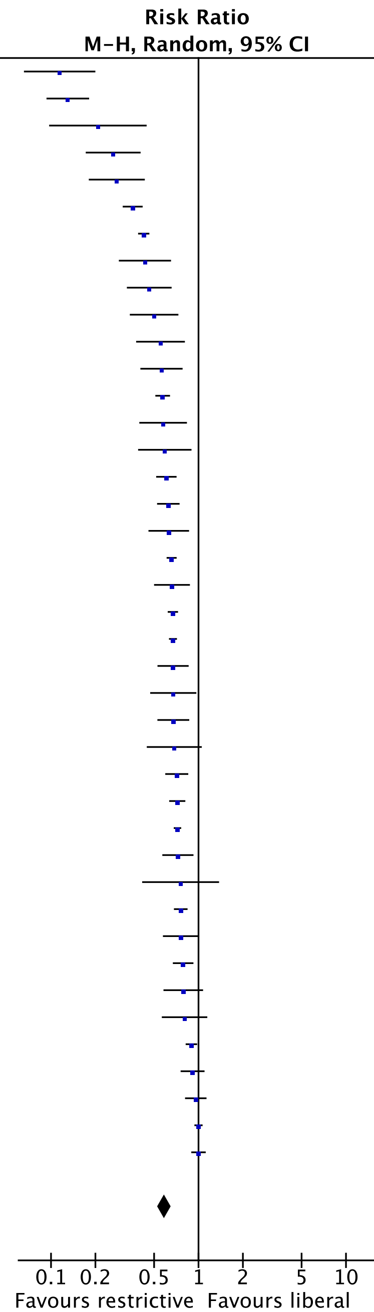
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition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

eFigure 9: Transfusion

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
Parker 2013	11	100	100	100	1.6%	0.11 [0.07, 0.20]	+	+	+	+	−	?	+
Prick 2014	33	261	251	258	2.3%	0.13 [0.09, 0.18]	+	+	+	+	−	+	+
Blair 1986	5	26	24	24	1.2%	0.21 [0.10, 0.44]	?	?	+	+	+	?	+
Lotke 1999	16	62	65	65	2.0%	0.26 [0.17, 0.40]	+	?	+	+	+	+	+
Carson 2013	15	55	55	55	2.0%	0.28 [0.18, 0.43]	+	+	+	+	+	+	+
Ducrocq 2021	122	342	323	324	2.8%	0.36 [0.31, 0.41]	+	+	+	+	+	+	+
Carson 2011	415	1009	974	1007	2.9%	0.43 [0.39, 0.46]	+	+	+	+	+	+	+
Gillies 2020	15	36	25	26	2.1%	0.43 [0.29, 0.64]	+	+	+	+	+	+	+
Carson 1998	19	42	41	42	2.2%	0.46 [0.33, 0.65]	+	+	+	+	+	?	+
Foss 2009	22	60	44	60	2.1%	0.50 [0.35, 0.72]	+	+	+	+	?	+	+
Cooper 2011	13	24	21	21	2.1%	0.55 [0.38, 0.80]	+	+	+	+	+	+	+
Hébert 1995	18	33	35	36	2.3%	0.56 [0.41, 0.77]	+	?	+	+	+	?	+
Villanueva 2013	219	444	384	445	2.8%	0.57 [0.52, 0.63]	+	+	+	+	+	?	+
Gobatto 2019	13	23	21	21	2.2%	0.58 [0.40, 0.82]	+	+	+	+	+	+	?
Shehata 2012	13	25	22	25	2.0%	0.59 [0.39, 0.88]	+	+	+	+	+	+	+
Hajjar 2010	118	249	198	253	2.8%	0.61 [0.52, 0.70]	+	+	+	+	+	+	+
Tay 2020	80	149	129	150	2.7%	0.62 [0.53, 0.73]	+	+	+	+	+	+	+
Laine 2018	22	40	35	40	2.3%	0.63 [0.46, 0.85]	?	−	+	+	+	?	+
Holst 2014	326	502	490	496	2.9%	0.66 [0.62, 0.70]	+	+	+	+	+	+	+
Møller 2019	19	29	29	29	2.4%	0.66 [0.51, 0.86]	+	+	+	+	+	+	?
Hébert 1999	280	418	420	420	2.9%	0.67 [0.63, 0.72]	+	+	+	+	+	?	+
Murphy 2015	637	1000	952	1003	2.9%	0.67 [0.64, 0.70]	+	+	+	+	+	+	+
Bergamin 2017	62	151	91	149	2.6%	0.67 [0.53, 0.85]	+	+	+	+	+	+	+
de Almeida 2015	33	101	47	97	2.2%	0.67 [0.48, 0.95]	+	+	+	+	+	+	+
So-Osman 2013	79	299	119	304	2.5%	0.67 [0.53, 0.85]	+	+	+	+	+	?	+
Topley 1956	8	12	10	10	2.0%	0.68 [0.45, 1.04]	?	?	+	+	−	−	+
Jairath 2015	133	403	247	533	2.7%	0.71 [0.60, 0.84]	+	−	+	+	+	?	+
Koch 2017	195	363	265	354	2.8%	0.72 [0.64, 0.80]	+	?	+	+	+	?	+
Mazer 2017	1271	2430	1765	2430	2.9%	0.72 [0.69, 0.75]	+	+	+	+	+	+	+
Bracey 1999	74	212	104	216	2.6%	0.72 [0.58, 0.91]	−	−	+	+	+	?	+
Nielsen 2014	11	30	16	33	1.5%	0.76 [0.42, 1.36]	+	+	+	+	+	+	?
Gregersen 2015	109	144	140	140	2.9%	0.76 [0.69, 0.83]	+	+	+	+	+	+	+
Johnson 1992	15	20	18	18	2.5%	0.76 [0.58, 0.99]	−	?	+	+	+	?	+
Walsh 2013	40	51	49	49	2.8%	0.79 [0.68, 0.91]	+	+	+	+	+	+	+
Fan 2014	41	96	52	96	2.4%	0.79 [0.59, 1.06]	+	+	+	+	+	+	+
Grover 2006	37	109	46	109	2.2%	0.80 [0.57, 1.13]	+	+	+	+	−	?	?
Palmieri 2017	141	168	166	177	2.9%	0.89 [0.83, 0.97]	+	+	+	+	+	+	+
Bush 1997	40	50	43	49	2.7%	0.91 [0.77, 1.08]	+	+	+	+	+	?	+
Webert 2008 (1)	26	29	29	31	2.7%	0.96 [0.82, 1.12]	+	+	+	+	+	?	+
DeZern 2016	59	59	30	30	2.9%	1.00 [0.95, 1.05]	+	+	+	+	+	+	+
Stanworth 2020	20	20	18	18	2.8%	1.00 [0.91, 1.10]	+	+	+	+	+	+	+
Total (95% CI)		**9676**		**9743**	**100.0%**	**0.60 [0.54, 0.66]**							
Total events	4825		7893										

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 1055.15$, df = 40 (P < 0.00001); $I^2 = 96\%$

Test for overall effect: Z = 9.74 (P < 0.00001)



Footnotes

(1) Three trials did not report the number of participants transfused; Kola -224...

Risk of bias legend

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

eTable 1. Details of studies contributing to data for adults in guidelines

(see also Cochrane review [Carson et al 2021)

In summary:
45 studies conducted in 370 sites in 24 countries. 42 studies contributed data to meta-analysis

- Recruitment commencement dates ranged from 1956 to 2017
- 20,599 participants at baseline
- Range of restrictive thresholds used: no transfusion to 9.7 g/dL
- Range of liberal thresholds used: <8g/dL to 12.5 g/dL

Study identifier / trial acronym (** indicates study data not used in meta-analysis)	Restrictive hemoglobin threshold	Liberal hemoglobin threshold	No. of participants (baseline)	Countries involved	No. of sites	Year recruitment began
Acute blood loss / trauma (6 studies)						
Jairath 2015 (TRIGGER)	<8 g/dL	<10 g/dL	936 (6 clusters)	UK	6	2012
Villanueva 2013	<7 g/dl	<9 g/dl	921	Spain	1	2003
Prick 2014 (WOMB)	Participants with HB between 4.8 and 7.9 received no transfusion	Participants with HB between 4.8 and 7.9 received transfusion	519	Netherlands	37	2004
Kola 2020	<7 g/dL	<8 g/dL	224	India	1	2015
Blair 1986	<8g/dl (or if in shock)	None	50	UK	1	Not stated
Topley 1956	Investigators estimated at least a litre of blood lost and attempted 'to leave the red cell volume at the end of	Investigators estimated at least a litre of blood lost and attempted 'to leave the red cell volume at the	22	UK	1	Not stated

Study identifier / trial acronym (** indicates study data not used in meta-analysis)	Restrictive hemoglobin threshold	Liberal hemoglobin threshold	No. of participants (baseline)	Countries involved	No. of sites	Year recruitment began
	resuscitation at 70-80 % of normal'	end of resuscitation at 100 % of normal or over'				
Cardiac (3 studies)						
Ducrocq 2021 (REALITY)	<8 g/dl	<10 g/dl	668	France; Spain	35	2016
Carson 2013 (MINT [pilot])	<8 g/dL (or if anemia apparent)	Patients... received 1 unit RBCs post randomization then were transfused any time HB fell < 10 g/dL	110	USA	8	2010
** Cooper 2011 (CRIT [pilot])	Hematocrit <24%	Hematocrit <30%	45	USA	2	2003
Cardiac surgery (8 studies)						
Mazer 2017 (TRICS III)	<7.5 g /dl	<9.5 g /dl in theatre or ICU OR <8.5 g/dl in non ICU ward	5092	* 19 countries	73	2014
Murphy 2015 (TITRe2)	<7.5 g /dl	<9 g /dl	2003	UK	17	2009
Koch 2017	Hematocrit trigger = 24%	Hematocrit trigger = 28%	722	USA; India	2	2007

Study identifier / trial acronym (** indicates study data not used in meta-analysis)	Restrictive hemoglobin threshold	Liberal hemoglobin threshold	No. of participants (baseline)	Countries involved	No. of sites	Year recruitment began
Hajjar 2010 (TRACS)	Hematocrit < 24%	Hematocrit < 30%	512	Brazil	1	2009
Bracey 1999	<8g/dl	<9 g/dL	428	USA	1	1997
Laine 2018	<8 g/dL	<10 g/dL	80	Finland	1	2014
Shehata 2012	<7 g/dl intraoperatively during cardiopulmonary bypass [CPB]; 7.5 g/dL or less postop	9.5 g/dL or less intraoperatively during CPB; less than 10 g/dL postop	50	Canada	1	2007
Johnson 1992	Hematocrit < or equal to 25%	Hematocrit < or equal to 32%	39	USA	1	Not stated
Critical care (including surgery within oncology) (8 studies)						
Holst 2014 (TRISS)	<7 g/dL	<9 g/dL	1005	Denmark; Sweden; Norway; Finland	32	2011
Hébert 1999 (TRICC)	<7 g/dL	<10 g/dL	838	Canada	25	1994
Palmieri 2017 (TRIBE)	<7 g/dl	<10 g/dl	345	USA (16 sites); Canada (1); New Zealand (1)	18	2010
Bergamin 2017 (TRICOP)	<7 g/dL	< 9 g/dL	300	Brazil	1	2012

Study identifier / trial acronym (** indicates study data not used in meta-analysis)	Restrictive hemoglobin threshold	Liberal hemoglobin threshold	No. of participants (baseline)	Countries involved	No. of sites	Year recruitment began
de Almeida 2015	<7 g/dL	< 9 g/dL	198	Brazil	1	2012
Walsh 2013 (RELIEVE [pilot])	<7 g/dL	<9g/dL	100	UK	6	2009
Hébert 1995	<7 to 7.5 g/dL	<10 to 10.5 g/dL	69	Canada	5	1993
Gobatto 2019	<7 g/dL	<9g/dl	47	Brazil	1	2014
Hematological malignancies (5 studies)						
Tay 2020	<7 g/dL	<9 g/dL	300	Canada	4	2011
DeZern 2016	<7 g/dL	<8g/dl	89	US	1	2014
Webert 2008	<8 g/dL	<12 g/dL	60	Canada	4	2003
Stanworth 2020 (REDDS)	Maintain pretransfusion Hb 8.5–10 g/dL	Maintain pretransfusion Hb 11.0–12.5 g/dL	38	UK; Australia; New Zealand	12	2015
** Jansen 2020 (TEMPLE)	<7.3 g/dL	<9.7 g/dL	19	Netherlands	3	2002
Orthopedic surgery (11 studies)						
Carson 2011 (FOCUS)	<8 g/dL or symptomatic anemia	<10 g/dL	2016	US; Canada	47	2004

Study identifier / trial acronym (** indicates study data not used in meta-analysis)	Restrictive hemoglobin threshold	Liberal hemoglobin threshold	No. of participants (baseline)	Countries involved	No. of sites	Year recruitment began
So-Osman 2013	Patients were assigned the most restrictive transfusion policy at the participating hospital. Threshold varied among the hospitals.	Patients were assigned the most liberal transfusion policy at the participating hospital. Threshold varied among the hospitals.	603	Netherlands	3	2001
Gregersen 2015	<9.7 g/dL; 6 mmol/L	<11.3 g/dL; 7 mmol/L	284	Denmark	1	2010
Grover 2006	<8 g/dL	<10 g/dL	260	UK	3	Not stated
Parker 2013	Participants with HB between 8.0 and 9.5 were selected. Restrictive group received no transfusion	Participants with HB between 8.0 and 9.5 were selected. Transfusion was automatic in this group until 10 g/dL reached	200	UK	1	2002
Fan 2014	<8 g/dL	<10 g/dL	192	China	1	2011
Lotke 1999	<9 g/dL	Automatic transfusion post knee replacement 'in anticipation of blood loss'	127	USA	1	Not stated
Foss 2009	<8 g/dL	<10 g/dL	120	Denmark	1	2004
Carson 1998	<8g/dl or symptomatic anemia	<10 g/dL	84	USA (3); UK (1)	4	1996
Nielsen 2014	<7.3 g /dl	<8.9 g /dl	66	Denmark	2	2009

Study identifier / trial acronym (** indicates study data not used in meta-analysis)	Restrictive hemoglobin threshold	Liberal hemoglobin threshold	No. of participants (baseline)	Countries involved	No. of sites	Year recruitment began
Gillies 2020 (RESULT-NOF)	<7 g/dl	<9 g/dl	62	UK	1	2017
Vascular surgery (2 studies)						
Bush 1997	<9 g/dL	<10 g/dL	99	USA	1	1995
Møller 2019	<8.0 g/dL	< 9.7 g/dL	58	Denmark	1	2015
Various cancers - non-hematological (2 studies)						
** Hoff 2011 (DAHANCA)	No transfusion	<13 for women; <14.5 for men	466	Denmark	Unclear	1986
Yakymenko 2018	<9·7 g/ dL	Differed by gender: for women, 11.5 g/ dL; for men: 13.1 g/dL	133	Denmark	1	2010

* Countries involved in TRICS- III (Mazer 2017). Majority USA. Also: Australia, Brazil, Canada, China, Colombia, Denmark, Egypt, Germany, Greece, India, Israel, Malaysia, New Zealand, Romania, Singapore, South Africa, Spain, Switzerland

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Details of studies contributing to data for children in guideline (see also Cochrane [Carson et al 2021] and TAXI reviews)

In summary:

- 7 studies conducted in 28 sites in 8 countries. 4 studies contributed data to meta-analyses conducted for this guideline
- Recruitment commencement dates ranged from 2001 to 2014
- 2,730 participants at baseline
- Range of restrictive thresholds used: <4g/dL to 9.7 g/dL
- Range of liberal thresholds used: up to 13 g/dL

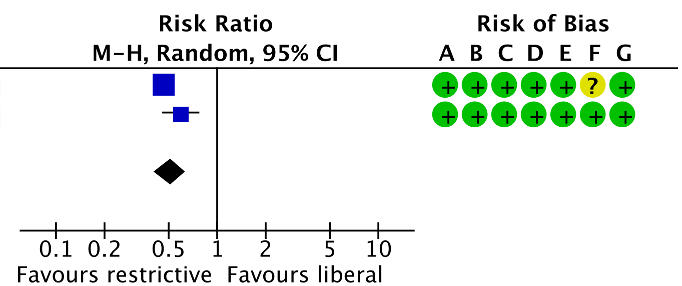
<u>Forest plots for 30-day mortality and morbidity outcomes in children</u>

eFigure 10: Transfusions

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Lacroix 2007	146	320	310	317	60.9%	0.47 [0.41, 0.53]
Cholette 2017	39	82	64	80	39.1%	0.59 [0.46, 0.77]
Total (95% CI)		**402**		**397**	**100.0%**	**0.51 [0.41, 0.65]**
Total events	185		374			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.88$, df = 1 (P = 0.09); $I^2 = 65\%$

Test for overall effect: Z = 5.64 (P < 0.00001)

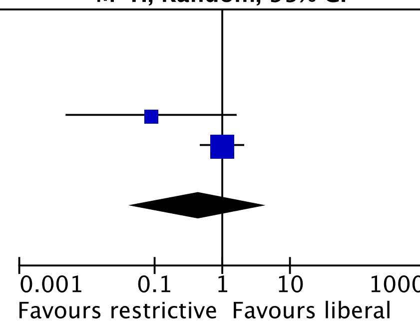


<u>Risk of bias legend</u>
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data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

eFigure 11: Mortality at 30 days (whole samples)

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Cholette 2011	0	30	0	30		Not estimable		? ? + + + ? +
Robitaille 2013	0	3	0	3		Not estimable		+ + + + + + +
de Gast-Bakker 2013	0	53	0	54		Not estimable		? ? ? + + ? +
Cholette 2017	0	82	5	80	33.8%	0.09 [0.00, 1.58]		+ + + + + + +
Lacroix 2007	14	320	14	317	66.2%	0.99 [0.48, 2.04]		+ + + + + ? +
Total (95% CI)		**488**		**484**	**100.0%**	**0.44 [0.04, 4.45]**		
Total events	14		19					

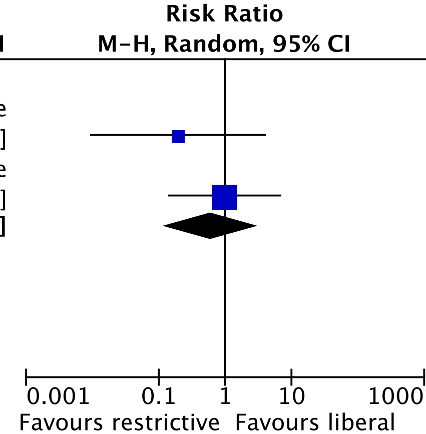
Heterogeneity: $Tau^2 = 1.98$; $Chi^2 = 2.72$, df = 1 (P = 0.10); $I^2 = 63\%$
Test for overall effect: Z = 0.70 (P = 0.49)



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): Objective measures
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

eFigure 12: Mortality at 30 days (cardiac subgroup only)

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
1.2.1 Cardiac surgery													
Cholette 2011	0	30	0	30		Not estimable	?	?	+	+	+	?	+
Cholette 2017	0	82	2	80	29.0%	0.20 [0.01, 4.00]	+	+	+	+	+	+	+
de Gast-Bakker 2013	0	53	0	54		Not estimable	?	?	?	+	+	?	+
Lacroix CARDIAC SUBGROUP	2	63	2	62	71.0%	0.98 [0.14, 6.77]	+	+	+	+	+	?	+
Subtotal (95% CI)		**228**		**226**	**100.0%**	**0.62 [0.12, 3.13]**							
Total events	2		4										
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 1 (P = 0.37); $I^2 = 0\%$													
Test for overall effect: Z = 0.58 (P = 0.56)													



Test for subgroup differences: Not applicable

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): Objective measures
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

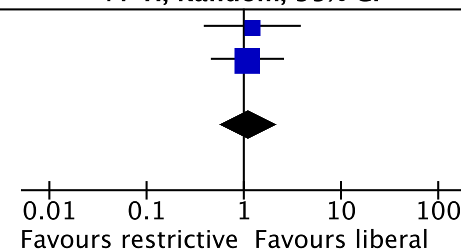
eFigure 13: Pneumonia

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI	A	B	C	D	E	F	G
de Gast-Bakker 2013	6	53	5	54	35.9%	1.22 [0.40, 3.76]	?	?	?	+	+	?	+
Lacroix 2007	11	320	10	317	64.1%	1.09 [0.47, 2.53]	+	+	+	+	+	?	+
Total (95% CI)		**373**		**371**	**100.0%**	**1.14 [0.58, 2.23]**							
Total events	17		15										

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Risk Ratio M-H, Random, 95% CI



Risk of bias legend

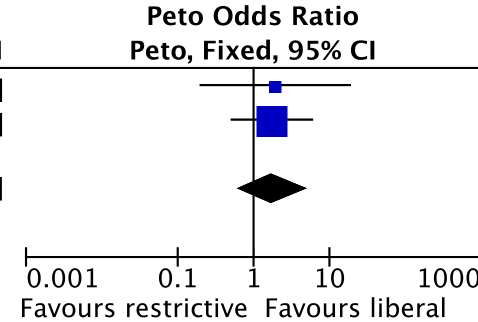
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Objective measures
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective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

eFigure 14: Thrombosis

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	A	B	C	D	E	F	G
Lacroix 2007	2	320	1	317	22.5%	1.93 [0.20, 18.65]	+	+	+	+	+	?	+
Cholette 2017	7	82	4	80	77.5%	1.74 [0.51, 5.91]	+	+	+	+	+	+	+
Total (95% CI)		**402**		**397**	**100.0%**	**1.78 [0.61, 5.22]**							
Total events	9		5										

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0\%$

Test for overall effect: Z = 1.06 (P = 0.29)



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): Objective measures

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

eTable 2.

Study identifier / trial acronym	Restrictive haemoglobin threshold	Liberal haemoglobin threshold	No. of particpants (baseline)	Countries involved	No. of sites	Year recruitment began
Cardiac surgery (3 discrete studies plus one subgroup analysis of a larger study)						
**Cholette 2011	< 9 g/dL trigger	13 g/dL trigger	62	USA	1	2006
**Cholette 2017	7.0 g/dL for biventricular repairs or 9.0 g/dL 'for palliative procedures plus a clinical indication'	9.5 g/dL for biventricular repairs or 12 g/dL 'for palliative procedures regardless of clinical indication'	162 [105 biventricular; 57 palliative]	USA	1	2012
**de Gast-Bakker 2013	<8 g/dL (5.0 mmol/l)	<10.8 g/dL (6.8 mmol/l)	107	Netherlands	1	2009
Willems 2010 (part of TRIPICU)	*[subgroup analysis of 125 participants of Lacroix 2007; see below]*					
Critical care (2 studies)						
* Akyildiz 2018	<7 g/dL	<10 g/dL	180	Turkey	1	2014
Lacroix 2007 (TRIPICU)	<7 g/dL	<9.5 g/dL	648	Canada; Belgium; USA; UK	19	2001
Hematological malignancies (1 study)						

Study identifier / trial acronym	Restrictive haemoglobin threshold	Liberal haemoglobin threshold	No. of particpants (baseline)	Countries involved	No. of sites	Year recruitment began
Robitaille 2013	<7 g/dL	<12 g/dL	6	Canada	1	2009
Uncomplicated severe anemia (HB of 4 to 6 g/dL) with no signs of clinical severity						
** Maitland 2019 (TRACT)	Participants with HB of 4 to 6 g/dL were recruited. Restrictive group received no transfusion unless new signs of clinical severity or a drop in hemoglobin occured to below 4g/dL	Participants with HB of 4 to 6 g/dL were recruited. 'Immediate' group received a transfusion (within this factorial trial this might be 20ml whole blood (or 10 ml of packed/ settled cells)) or 30 ml whole blood (or 15 ml of packed /settled cells), per kg body weight)	1565	Uganda; Malawi	4	2014

* trial data were used within meta-analysis within 2021 Cochrane review but data were not suitable for guideline outcomes

** trial data were not used within meta-analysis within 2021 Cochrane review but will appear in a future update

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