Title page

Article title:

Effect of restrictive versus liberal red cell transfusion strategies on haemostasis: systematic review and meta-analysis

Short title:

Bleeding and red cell transfusion meta-analysis

***Co-authors*:**

Ms Katherine S Colman

Monash University Medical School, Melbourne, Australia

kscol1@student.monash.edu

Dr Babette W Prick MD PhD

Department of Obstetrics and Gynaecology, Erasmus Medical Centre, Rotterdam, the Netherlands

babette_prick@hotmail.com

Dr Johannes J Duvekot MD PhD

Department of Obstetrics and Gynaecology, Erasmus Medical Centre, Rotterdam, the Netherlands

J.J.Duvekot@erasmusmc.nl

Dr Connor Sweeney MRCP

Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford,

United Kingdom

Connor.sweeney@ouh.nhs.uk

Dr Ayodele Odutayo MD

Centre for Statistics in Medicine, University of Oxford, United Kingdom

Ayodele.odutayo@mail.utoronto.ca

Dr Vipul Jairath MRCP DPhil

Departments of Medicine, Epidemiology and Biostatistics, Western University, London, Ontario, Canada

Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

vjairath@uwo.ca

Dr Carolyn Doree PhD

Systematic Review Initiative, NHS Blood and Transplant, Oxford, United Kingdom

Carolyn.doree@nhsbt.nhs.uk

Dr Marialena Trivella DPhil

Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom

Marialena.trivella@csm.ox.ac.uk

Dr Sally Hopewell DPhil

Oxford Clinical Trials Research Unit, Nuffield Department of Orthopaedics, University of Oxford, United Kingdom

Sally.hopewell@csm.ox.ac.uk

Dr Lise J Estcourt MRCP FRCPath DPhil

NHS Blood and Transplant, Oxford, United Kingdom

Oxford Clinical Research in Transfusion Medicine, University of Oxford, United Kingdom

Lise.estcourt@ndcls.ox.ac.uk

Dr Simon J Stanworth MRCP FRCPath DPhil

NHS Blood and Transplant/Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

Oxford Clinical Research in Transfusion Medicine, University of Oxford, United Kingdom

Simon.stanworth@nhsbt.nhs.uk

***Corresponding author*:**

Dr Michael J R Desborough MRCP FRCPath

NHS Blood and Transplant, Oxford, United Kingdom

Oxford Clinical Research in Transfusion Medicine, University of Oxford, United Kingdom

Michael.desborough@ouh.nhs.uk

Postal address: NHS Blood and Transplant, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU, United Kingdom

Phone: +44 7736 843592

Fax: +44 1865 387957

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What is known about this topic?
• *In vitro* data suggest that red cells play a key role in haemostasis but there is little clinical data to support this
What this paper adds
• This meta-analysis evaluated whether aiming for a higher haemoglobin concentration reduces the risk of bleeding • Aiming for a higher haemoglobin concentration did not reduce the risk of bleeding and in some settings may increase it • There is no evidence to support the use of liberal red cell transfusion to reduce bleeding risk

Summary

Red cells play a key role in normal haemostasis *in vitro* but their importance clinically is less clear. The objective of this meta-analysis was to assess if correction of anaemia by transfusing red cells at a high haemoglobin threshold (liberal transfusion) is superior to transfusion at a lower haemoglobin threshold (restrictive transfusion) for reducing the risk of bleeding or thrombotic events. We searched for randomized controlled trials in any clinical setting that compared two red cell transfusion thresholds and investigated the risk of bleeding. We searched for studies published up to 19th October 2016 in The Cochrane Central Register of Controlled Trials, MEDLINE, PubMed, Embase, and the Transfusion Evidence Library and ISI Web of Science. Relative risks (RR) or Peto Odds Ratios (pOR) were pooled using a random-effect model. Nineteen randomized trials with 9852 participants were eligible for inclusion in this review. Overall there was no difference in the risk of any bleeding between transfusion strategies (RR 0.91, 95% confidence interval [CI] 0.74 to 1.12). The risk of severe or life-threatening bleeding was lower with a restrictive strategy (RR 0.75, 95% CI 0.57 to 0.99). There was no difference in the risk of thrombotic events (RR 0.83, 95% CI 0.61 to 1.13). The risk of any bleeding was not reduced with liberal transfusion and there was no overall difference in the risk of thrombotic events. Data from the included trials do not support aiming for a high haemoglobin threshold to improve haemostasis. PROSPERO registration number CRD42016035519.

Key words

Haemorrhage, myocardial infarction, transfusion, stroke, venous thromboembolism

Introduction

There is an increasing body of laboratory evidence indicating the role of red cells in promoting normal haemostasis [1-6]. Anaemia has been associated with a prolonged bleeding time [7, 8], with correction of anaemia normalising the results [9]. Conversely, erythrocytosis is associated with the risk of pathological thrombus formation [10]. Red cell transfusion remains the most readily available means for rapid correction of anaemia with laboratory studies demonstrating that red cell transfusion may promote haemostasis [11, 12]. In many settings, re-bleeding after an initial bleeding event is associated with an increased risk of mortality [13, 14] and some physicians opt to transfuse red cells or correct anaemia with an aim to improve haemostasis [15]. However clinical data on whether correction of anaemia prevents bleeding are sparse. Consequently, there is a scientific and clinical need to determine whether transfused red cells improve haemostasis and reduce the risk of bleeding.

An increasing number of studies have been performed randomizing patients to a liberal or restrictive transfusion threshold. Data from these trials provide an opportunity to assess if adjustment of haemoglobin concentration with red cell transfusion reduces the risk of bleeding, providing an opportunity to examine the importance of red cell in haemostasis clinically.

This meta-analysis was undertaken to evaluate the impact of liberal and restrictive red cell transfusion strategies on outcomes of bleeding and thrombotic events.

Materials and methods

This systematic review followed the methods in the prospectively registered protocol:

PROSPERO number CRD42016035519. Methodology was consistent with the definitions from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [16].

Eligibility criteria

We only included randomized controlled trials (RCTs). There was no restriction on the indication for transfusion or the underlying disease. Trials were eligible for inclusion if they evaluated the effectiveness of any policy involving the use of a trigger or transfusion threshold based on haemoglobin concentration (Hb) for guiding allogeneic red cell transfusion. Control group patients were required to receive transfusion at a higher Hb. We made a post-hoc decision to exclude trials which had a difference in Hb threshold of less than 20 g/l to ensure consistency between studies.

Primary outcome:

Risk of any bleeding: this included all bleeding of World Health Organization (WHO) grade two or above (supplementary material).

Secondary outcomes:

1. Risk of severe or life-threatening bleeding: any bleed equivalent to WHO grade three or more.
2. Risk of fatal bleeding
3. Time from randomization to first bleed
4. Risk of thrombotic events (myocardial infarction, ischemic stroke, or arterial or venous thromboembolism).

We did not assess mortality, as this has been the focus of two other high quality systematic reviews [17, 18].

Search strategy

We searched for RCTs in the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2016, Issue 9), MEDLINE (OvidSP, from 1946), PubMed (for epublications ahead of print), Embase (OvidSP, from 1974), the Transfusion Evidence Library (from 1950) and ISI Web of Science: Conference Proceedings Citation Index - Science (from 1990) on 19th October 2016. There were no search restrictions on date, language, or publication status.

Data extraction

Trial selection

Two independent review authors initially used an online systematic review management tool (Covidence; https://www.covidence.org/) to screen all electronically-derived citations and abstracts of papers identified by the review search strategy for relevance. Studies clearly irrelevant were excluded at this stage.

The full texts of all potentially relevant trials were then formally assessed for eligibility by two independent review authors against the criteria outlined above. All disagreements were resolved by discussion with the other authors. Further information was sought from study authors when an article contained insufficient data to make a decision about eligibility. The reasons why potentially relevant studies failed to meet the eligibility criteria were recorded.

Risk of bias assessment and grading the quality of evidence

We assessed the risk of bias using the methods outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions [19]. Risk of bias was assessed as high, low, and unclear for each of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Risk of bias was also assessed from the way bleeding and thrombotic events were reported: low risk trials pre-specified bleeding or thrombotic events as outcomes and defined bleeding or thrombotic events clearly. Unclear trials either did not pre-specify bleeding or thrombotic events as outcomes or did not report a clear definition of bleeding or thrombotic events. High risk trials did not define bleeding or thrombotic events equally in both arms of the trial.

We assessed the quality of evidence for outcomes of any bleeding, severe or life-threatening bleeding, fatal bleeding and thrombotic events according to GRADE criteria. GRADE quality was classified as very low, low, moderate, or high [20].

Data synthesis and analysis

All statistical analyses were performed using Review Manager 5.3 and presented as forest plots. When meta-analysis was feasible, we used the random-effect model and the Mantel-Haenszel method for pooling the data. We used a random effect model as we anticipated that there would be heterogeneity in the finding between studies. We reported risk ratios (RR) for dichotomous outcomes, with 95% confidence intervals (CI). Peto odds ratio (pOR) was used for outcomes with low event rates (less than 5%). Hazard ratios (HR) with 95% confidence intervals were presented for time to event outcomes.

Where appropriate we calculated number needed to treat (NNTT). We inspected funnel plots for the presence of small study effects.

Assessment of heterogeneity

Clinical heterogeneity was examined by assessing subgroups: underlying disease (e.g. gastrointestinal bleeding). Statistical heterogeneity of treatment effects between trials was assessed using a Chi^2 test with a significance level at $P < 0.1$. The I^2 statistic was used to quantify the percentage of variability that was due to heterogeneity (we defined heterogeneity of >50 to 80% as moderate and >80% as substantial). Sensitivity analyses were performed by: assessing results without children; using published full text papers only; and only using trials considered to be at low risk of bias from blinding of study analysts. Each of these analyses was pre-specified in the review protocol.

Results

Search results

Figure 1 shows the flow of studies through the review. The search retrieved 10,823 results and one further trial was identified from the references of other reviews. This was reduced to 8,742 when duplicates were removed and reduced to 74 trials following screening of titles and abstracts. 55 trials were excluded with 28 not reporting bleeding or thrombotic events as outcomes, 13 having a difference in target haemoglobin of less than 20 g/l, five assessing the wrong intervention, three wrong study design, five secondary citations, and one incorrect comparator. Details of the 13 trials excluded with a difference in target haemoglobin of less than 20 g/l are included in the appendices. The final data set for meta-analysis consisted of 19 trials and 9,854 participants [21-39].

Unpublished data

One trial was included after obtaining unpublished data from the original authors [37]. Unpublished data on severity of bleeding was obtained from the original authors of one trial [38] and we had access to individual participant data from the cluster randomized trial to calculate the intraclass correlation coefficient for bleeding [29]. The intraclass correlation coefficient was 0.006 for bleeding, suggesting that nearly all the effect was due to differences between participants, rather than between clusters. We performed a sensitivity analysis without taking the clustering into account, and this did not alter our results. These data were therefore included as unique patient data.

Trial characteristics

The setting of the included trials were: gastrointestinal bleeding (three trials) [29, 31, 36], intensive care (five trials) [27, 28, 30, 34, 37], haematological malignancy undergoing intensive chemotherapy or stem cell transplantation (one trial) [38], surgery (nine trials) [22-26, 32, 33, 35, 39], and cardiac catheterisation (one trial) [21]. Included studies were both multi-centre (11 trials) [21, 22, 26-30, 32, 34, 37, 38] and single centre (eight trials) [23-25, 31, 33, 35, 36, 39]. Ten of the 19 trials used leukocyte-reduced red cells [21-23, 26, 28, 34, 36-39].

Transfusion strategies

There was variation in the red cell transfusion thresholds used to define liberal and restrictive transfusion arms between trials (Characteristics of included studies are reported in Table 1). The liberal transfusion thresholds used in the included trials were between an Hb of 89g/ and 120g/l; and the restrictive transfusion thresholds were between an Hb of 70 and 80g/l. No trial had a restrictive threshold between 81-88g/l.

Mean Hb and exposure to red cell transfusion were lower in all trials in restrictive transfusion threshold arms than in the liberal transfusion threshold arms. The difference in Hb between groups was statistically significant in 15/19 trials [21-24, 26-28, 30, 32, 34-39], and the difference in red cell transfusions was statistically significant in 15/19 trials [21-25, 27, 28, 30, 32, 34-39].

Definitions of bleeding and thrombotic events

The definition of bleeding varied between trials (supplementary material). Bleeding was pre-specified as an outcome in four trials but was not the primary outcome. One trial reported bleeding using the WHO bleeding scale [38] and we categorized bleeding outcomes in the remaining trials to the most appropriate WHO bleeding grade.

Thrombotic events included myocardial infarction, ischemic stroke, and venous or arterial thromboembolism. There was variation between trials on which of these outcomes were reported and the methods used to define these outcomes (supplementary material).

Effects on outcomes

Risk of any bleeding

Overall there was no difference in risk of any bleeding in the restrictive transfusion arms compared with the liberal transfusion arms (RR 0.91, 95% CI 0.74 to 1.12, I^2 = 37%, 12 trials, 7614 participants, Figure 2) [22, 28-38]. The sensitivity analyses and results including trials that were excluded post-hoc supported the results of the main analysis. There was no evidence of publication bias. The GRADE quality of evidence was judged to be moderate (Table 2).

We performed subgroup analysis assessing different clinical settings. There was evidence of subgroup differences (I^2 = 55.8%, p = 0.08). In the setting of acute upper gastrointestinal bleeding, there was a lower risk of any bleed in the restrictive transfusion arm compared to the liberal transfusion arm (RR 0.64, 95% CI 0.48 to 0.86, I^2 = 0%, three trials, 1592 participants) [29, 31, 36]. No difference was found in the risk of any bleeding in the remaining subgroups.

Risk of severe or life-threatening bleeding

Overall the risk of severe or life-threatening bleeds was slightly lower in the restrictive transfusion arms compared with the liberal transfusion arms (RR 0.75, 95% CI 0.57 to 0.99, I^2 = 32%, 11 trials, 7564 participants, Figure 3) [22, 28-34, 36-38]. The sensitivity analyses supported the results of the main analysis. There was no difference in the risk of severe or life-threatening bleeding if the trials that were excluded post-hoc were included in the analysis (RR 0.92, 95% CI 0.71 to 1.20, I^2 = 44%, 19 trials, 9280 participants). There was no evidence of publication bias. Overall, the NNTT to prevent one severe or life-threatening bleed was 57 (95% CI 36.6 to 122.5). The GRADE quality of evidence was judged to be moderate (Table 2).

We performed subgroup analyses assessing different clinical settings. There was no evidence of subgroup differences (I^2 = 18.3%, p = 0.30). The risk of severe or life-threatening bleeding was lower in the subgroup with acute gastrointestinal bleeding (RR 0.57, 95% CI 0.41 to 0.78, I^2 = 0%, three trials, 1592 participants, Figure 4) [29, 31, 36]. No difference was found in the risk of severe or life-threatening bleeding in the remaining subgroups. To prevent one severe or life-threatening bleed in gastrointestinal bleeding

the NNTT was 21 (95% CI 13.1 to 50.9).

Risk of fatal bleeding

Overall the risk of fatal bleeding was lower in the restrictive transfusion arms compared with the liberal transfusion arms (pOR 0.35, 95% CI 0.15 to 0.81, I^2 = 0%, five trials, 3648 participants) [29, 32, 33, 35, 36]. However the small number of studies and predominance of trials in the gastrointestinal bleeding category limits the generalizability of this result. Inclusion of trials that were excluded post-hoc supported the results of the main analysis. The GRADE quality of evidence was judged to be very low (Table 2).

We performed subgroup analysis assessing different clinical settings. There was no evidence of subgroup differences (I^2 = 0%, p = 0.43). Restrictive transfusion resulted in fewer participants with fatal bleeding in the subgroup with acute gastrointestinal bleeding (pOR 0.31, 95% CI 0.13 to 0.76, I^2 = 0%, two trials, 1529 participants) [29, 36]. No difference was found in fatal bleeding for surgery. The NNTT to prevent one fatal bleed in the gastrointestinal bleeding subgroup was 74 (95% CI 40.8 to 369.2).

Time from randomization to first bleed

Time to first bleed was reported in one trial for patients with haematological malignancies undergoing intensive chemotherapy. Median time to first bleed reported from the study was eight days in the restrictive arm and five days in the liberal transfusion arm: (HR 1.07, 95% CI 0.59 to 1.94, one trial, 60 participants) [38].

Risk of thrombotic events

Overall there was no difference in the risk of thrombotic events in the restrictive

transfusion arms compared with the liberal transfusion arms (RR 0.83, 95% CI 0.61 to 1.13, I^2 = 42%, 9381 participants, 17 trials, Figure 4) [21-30, 32-37, 39]. The sensitivity analyses and results including trials that were excluded post-hoc supported the results of the main analysis. There was no evidence of publication bias. The GRADE quality of evidence was judged to be moderate (Table 2).

We performed subgroup analysis assessing different clinical settings. There was no evidence of subgroup differences (I^2 = 43.7%, p = 0.15). No difference was found in the risk of a thrombotic event in the subgroups.

No difference was found in the risk of ischaemic stroke (pOR 0.71, 95% CI 0.46 to 1.10, I^2 = 16%, 13 trials, 7622 participants) [21-25, 28, 30, 32, 34-37, 39], myocardial infarction (pOR 1.10, 95% CI 0.78 to 1.56, I^2 = 54%, 13 trials, 7879 participants) [21-28, 32, 34-37], or venous thromboembolism (pOR 0.69, 95% CI 0.44 to 1.07, I^2 = 9%, 11 trials, 3418 participants) [21-26, 33-35, 37, 39].

Risk of bias

The risk of bias is summarized in Figures 2 to 4. Blinding of outcome assessors was considered at high risk of bias in six trials [29, 30, 35-37, 39] and at unclear risk of bias in a further five trials [24-27, 31]. The definition of bleeding was considered to be at high risk of bias in one out of 12 trials that reported bleeding [37] and at unclear risk of bias in a further seven trials [22, 28, 30, 32-35]. The definition of a thrombotic event was considered to be at high risk of bias in one out of 17 trials that reported thrombotic events [29] and at unclear risk of bias in a further ten trials [24-27, 30, 33, 34, 36, 37, 39].

Discussion

We identified 19 randomized controlled trials that enrolled 9854 participants randomized to a maintaining a low, or higher haemoglobin concentration with red cell transfusion (restrictive or liberal red cell transfusion policy). Across all trials, a liberal transfusion threshold was not associated with lower risk of bleeding, severe or life-threatening bleeding, fatal bleeding, or thrombotic events compared to a restrictive transfusion threshold. Restrictive red cell transfusion resulted in a lower risk of severe or life-threatening bleeding and fatal bleeding than liberal transfusion. The lack of a difference in rates of thrombotic events combined with a decrease in the risk of bleeding with a restrictive transfusion threshold suggests that any haemostatic effect from transfusing red cells is equalled, or outweighed by risks of transfusion.

Heterogeneity between trials was low to moderate and the quality of the evidence by GRADE criteria was very low to moderate.

In our review, subgroup analysis of participants with acute upper gastrointestinal bleeding indicated that they might specifically benefit from restrictive transfusion practice. These patients can be vulnerable to re-bleeding due to fluid overload and elevated portal venous pressure which is more common with liberal red cell transfusion [36, 40, 41].

Previous systematic reviews reported no difference in the risk of thromboembolism or 30-day mortality when a restrictive transfusion is used in place of a liberal transfusion regimen [18, 28, 42]; although a separate review assessing the subgroups of participants with known cardiovascular disease noted an increased risk of myocardial infarction with

restrictive transfusion [43]. These findings are consistent with the results of this review. However, our results are at variance with *in vitro* data which demonstrates the essential role that red cells play in normal haemostasis [1-6]. It is possible that changes in circulating volume following red cell transfusion may increase the risk of bleeding, negating any potential benefits from increasing the number of circulating red cells.

Limitations

There was diversity in the clinical settings across all trials, and some settings such as haematological malignancies were not well represented by the published evidence. The post-hoc decision to include only trials with a haemoglobin difference of at least 20 g/l between arms reduced variability between the studies. Results were similar before and after the post-hoc exclusion with the exception of the risk of severe or life-threatening haemorrhage where no difference was found between the arms when the trials that were excluded post-hoc were included. We found no benefit in liberal transfusion to prevent severe or life-threatening bleeding. However it is less clear whether there is an increase in severe or life-threatening bleeding with liberal transfusion, as the results are largely driven by the inclusion of patients with acute gastrointestinal bleeding (who gain greatest benefit from restrictive transfusion thresholds). Definitions of outcomes varied between trials with bleeding pre-defined as an outcome in only 4/12 studies that reported it. The pattern was similar for thrombotic events where it was only pre-specified as an outcome in 8/17 studies that reported it. The duration that participants received the intervention and the transfusion thresholds varied between trials. Risk of bias from inadequate blinding of participants, clinicians, and outcome assessors may also limit the effect estimate. For fatal bleeding the event rate was low, placing this outcome at risk of imprecision.

Conclusion

The results of this review indicate that the use of higher Hb thresholds for triggering transfusion (most commonly 90 to 100 g/l) does not improve bleeding outcomes compared to lower Hb thresholds (most commonly 70 to 80 g/l). In the subgroup of patients with gastrointestinal bleeding, restrictive red cell transfusion policies resulted in lower risk of severe or life-threatening bleeding and fatal bleeding than liberal transfusion policies. There was no difference in the risk of thrombotic events. Overall, these findings do not support the use of targeting a higher haemoglobin concentration with liberal red cell transfusion to prevent bleeding.

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Disclosure of conflicts of interest

MD, KC, CS, AO, CD, MT, SH, LE and SS have no conflicts of interest to declare. BP, JD, and VJ are each authors of one of the original studies included in this review.

Contributions

MD wrote the manuscript. MD, KC and CS extracted data from published trials. AO analysed the intracluster correlation coefficient for the cluster randomized trial. CD constructed the search strategy. MT analysed the statistics. SH provided methodological expertize. MD, LE and SS formulated the ideas for this study. BP, JD and VJ provided and

analysed unpublished data from their studies which were incorporated into this review.

All authors critically appraised and revised the manuscript.

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Table legends

Table 1. Characteristics of included studies. [1]abstract only, [2]median (range), [3]median (95% confidence interval), [4]liberal threshold, increased to 120g/l and restrictive threshold to 90g/l for palliative procedures, [5]liberal transfusion threshold increased to

100g/l and restrictive to 75g/l after cardiopulmonary bypass, ACS – acute coronary syndrome, AUGIB - acute upper gastrointestinal bleeding, CARE - cardiac anaesthesia risk evaluation, ICU - intensive care unit, L - liberal transfusion threshold and R - restrictive transfusion threshold.

Table 2. GRADE quality of evidence. CI - Confidence Interval, Hb – haemoglobin, HR - Hazard Ratio, pOR - Peto Odds Ratio, RCT - Randomized Controlled Trial, RR - Risk Ratio. [1]Quality of evidence downgraded one point for risk of bias as not all participants, personnel, and outcome assessors blinded. [2]Quality of evidence downgraded one point for imprecision due to low number of events. [3]Quality of evidence downgraded one point for indirectness.

Figure legends

Figure 1. Study flow diagram

Figure 2. Forest plot of risk of any bleeding. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals. Risk of bias categories were: (A) Sequence generation, (B) Allocation concealment, (C) Blinding of participants and personnel, (D) Blinding of outcome assessors, (E) Incomplete outcome data, (F) Selective outcome reporting, (G) Other sources of bias, and (H) Bleeding definition. High risk of bias for a category is indicated by −, unclear risk of bias by ? and low risk of bias by +.

Figure 3. Forest plot of risk of severe or life-threatening bleeding. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals. Risk of bias categories were: (A) Sequence generation, (B) Allocation concealment, (C) Blinding of participants and personnel, (D) Blinding of outcome assessors, (E) Incomplete outcome data, (F) Selective outcome reporting, (G) Other sources of bias, and (H) Bleeding definition. High risk of bias for a category is indicated by −, unclear risk of bias by ? and low risk of bias by +.

Figure 4. Forest plot of risk of thrombotic events. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals. Risk of bias categories were: (A) Sequence generation, (B) Allocation concealment, (C) Blinding of participants and personnel, (D) Blinding of outcome assessors, (E) Incomplete outcome data, (F) Selective outcome reporting, (G) Other sources of bias, and (H) Thrombotic event definition. High risk of bias for a category is indicated by −, unclear risk of bias by ? and low risk of bias by +.

Tables

Table 1.

Trial [Country]	Setting	Threshold	n	Age in years mean ± standard deviation or median (interquartile range)	Gender (M/F)	Haemoglobin transfusion threshold (g/L)
Carson 2011 [22] [Canada & USA]	Surgical repair of hip fracture in patients with cardiovascular disease	L	1007	81.8 ± 8.8	239/770	100
		R	1009	81.5 ± 9.0	250/757	80
Carson 2013 [21] [USA]	ACS or stable angina undergoing cardiac catheterization	L	55	67.3 ± 13.6	28/27	100
		R	55	74.3 ± 11.1	27/28	80
Cholette 2016 [39] [USA]	Infants undergoing cardiac surgery	L	80	43 (1 to 730)[2] days	45/35	95[4]
		R	82	84 (2 to 914)[2] days	40/42	70[4]
De Almeida 2015 [23] [Brazil]	Major oncological surgery requiring ICU admission	L	97	64 ± 14	55/42	90
		R	101	64 ± 12	55/46	70
Fan 2014 [24] [China]	Elective total hip replacement	L	92	75 ± 6	33/59	100
		R	94	73 ± 7	30/64	80
Foss 2009 [25] [Denmark]	Hip fracture surgery	L	60	81 ± 6.8	14/46	100
		R	60	81 ±7.3	14/46	80
Grover 2006 [26] [UK]	Lower limb arthroplasty	L	109	71.5 ± 7.6	55/54	100
		R	109	70.7 ± 7.1	48/61	80
Hébert 1999 [27] [Canada]	ICU patients	L	420	58.1 ± 18.3	255/165	100
		R	418	57.1 ± 18.1	269/149	70
Holst 2014 [28] [Denmark, Finland, Norway & Sweden]	ICU patients with septic shock	L	497	67 (58 to 75)	259/237	90
		R	503	67 (57 to 73)	272/230	70
Jairath 2015 [29] [UK]	AUGIB (cluster randomized)	L	533	60.4 ± 20.0	322/211	100
		R	403	58.0 ± 20.3	244/159	80
Lacroix 2007 [30] [Canada]	Paediatric patients in ICU	L	317	3.3 ± 4.3	191/126	95
		R	320	3.0 ± 3.9	190/130	70
Lee 2014 [31][1] [South Korea]	AUGIB	L	31	-	-	100
		R	32	-	-	80
Murphy 2015 [32] [UK]	Non-emergency cardiac surgery	L	1003	70.8 (64.1 to 76.7)	680/323	90
		R	1000	69.9 (63.1 to 76.0)	693/307	75
Nielsen 2014 [33]	Hip-replacement revision surgery	L	33	72 (53 to 89)[3]	20/13	89

Outcome	Number of participants	GRADE quality of evidence	Study event rates (%)		Relative risk (95% CI)	Absolute risk (95% CI)
			Restrictive transfusion (Hb 80 to 90 g/l)	Liberal transfusion (Hb 89 to 120g/l)		
Any bleeding	7614 (12 RCTs)	⊕⊕⊕◯ MODERATE[1]	303/3746 (8.1%)	348/3868 (9.0%)	**RR 0.91** (0.74 to 1.12)	**8 fewer per 1000** (23 fewer to 11 more)
Severe or life-threatening bleeding	7564 (11 RCTs)	⊕⊕⊕◯ MODERATE[1]	144/3721 (3.9%)	217/3843 (5.6%)	**RR 0.75** (0.57 to 0.99)	**14 fewer per 1000** (24 fewer to 1 fewer)
Fatal bleeding	3648 (5 RCTs)	⊕◯◯◯ VERY LOW[1,2,3]	5/1759 (0.3%)	17/1889 (0.9%)	**pOR 0.35** (0.15 to 0.81)	**6 fewer per 1000** (8 fewer to 2 fewer)
Time from randomisation to first bleed	60 (1 RCTs)	⊕◯◯◯ VERY LOW[1,2,3]	-	-	**HR 1.07** (0.59 to 1.14)	-
Thrombotic events	9381 (17 RCTs)	⊕⊕⊕◯ MODERATE[1]	179/4630 (3.9%)	215/4751 (4.5%)	**RR 0.83** (0.61 to 1.13)	**8 fewer per 1000** (18 fewer to 6 more)

[Denmark]		R	33	68 (43 to 96)[3]	16/17	73
Robertson 2014 [34] [USA]	Severe traumatic brain injury	L	101	31 (24 to 45)	88/13	100
		R	99	28 (21 to 48)	85/14	70
Shehata 2012 [35] [Canada]	Cardiac surgery with CARE score 3 or 4	L	25	68.8 ± 9.2	20/5	95[5]
		R	25	67.2 ± 11.2	17/8	70[5]
Villanueva 2013 [36] [Spain]	AUGIB	L	445	66 ± 15	291/154	90
		R	444	64 ± 16	314/130	70
Walsh 2013 [37] [UK]	Mechanically ventilated, patients in ICU	L	49	68 ± 8	24/25	90
		R	51	67 ± 7	36/15	70
Webert 2008 [38] [Canada]	Intensive chemotherapy for acute leukaemia or stem cell transplantation	L	31	45.3 ± 16.8	14/17	120
		R	29	50.8 ± 15.3	18/11	80

Table 2.