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

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Abstract

Background—Most clinical practice guidelines recommend restrictive red cell transfusion practices, with the goal of minimising exposure to allogeneic blood. The purpose of this review is to compare clinical outcomes in patients randomised to restrictive versus liberal transfusion thresholds (triggers).

Objectives—To examine the evidence for the effect of transfusion thresholds on the use of allogeneic and/or autologous red cell transfusion, and the evidence for any effect on clinical outcomes.

Search methods—We identified trials by searching: the Cochrane Injuries Group Specialised Register (searched 1 February 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1), MEDLINE (Ovid) 1948 to January Week 3 2011, EMBASE (Ovid) 1980 to 2011 (Week 04), ISI Web of Science: Science Citation Index Expanded (1970 to February 2011) and ISI Web of Science: Conference Proceedings Citation Index - Science (1990 to February 2011). We checked reference lists of other published reviews and relevant papers to identify any additional trials.

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CONTRIBUTIONS OF AUTHORS

Contributors (names are listed alphabetically):

Paul Carless (University of Newcastle) performed original database literature searches, screened abstracts and titles for relevant articles, obtained relevant papers, applied inclusion/exclusion criteria to retrieved papers, extracted data from the trials, quality assessed trials, entered data into Meta-View 4.1, entered all study details into Review Manager 5.1, and co-wrote the review; Jeffrey Carson (Robert Wood Johnson Medical School) for the 2011 update, screened abstracts and titles for relevant articles, obtained relevant papers, applied inclusion/exclusion criteria to retrieved papers, extracted data from the trials, quality assessed trials, entered data into Meta-View 4.1, entered all study details into Review Manager 5.1, and co-wrote review; Paul Hebert (Ottawa General Hospital) reviewed the manuscript, provided expertise with analysis and content expert opinion.

DECLARATIONS OF INTEREST

Dr. Carson reports receiving grant support to his institution from Amgen and US National Institutes of Health. He is involved with guideline development. Dr. Hebert reports receiving grant support from Amgen and Johnson and Johnson.

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Selection criteria—Controlled trials in which patients were randomised to an intervention group or to a control group. We included trials where intervention groups were assigned on the basis of a clear transfusion 'trigger', described as a haemoglobin (Hb) or haematocrit (Hct) level below which a red blood cell (RBC) transfusion was to be administered.

Data collection and analysis—We pooled risk ratios of requiring allogeneic blood transfusion, transfused blood volumes and other clinical outcomes across trials using a random-effects model. Two people performed data extraction and assessment of the risk of bias.

Main results—We included 19 trials involving a total of 6264 patients and they were similar enough that results could be combined. Restrictive transfusion strategies reduced the risk of receiving a RBC transfusion by 39% (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.52 to 0.72). This equates to an average absolute risk reduction (ARR) of 34% (95% CI 24% to 45%). The volume of RBCs transfused was reduced on average by 1.19 units (95% CI 0.53 to 1.85 units). However, heterogeneity between trials was statistically significant ($P < 0.00001$; $I^2 \geq 93\%$) for these outcomes. Restrictive transfusion strategies did not appear to impact the rate of adverse events compared to liberal transfusion strategies (i.e. mortality, cardiac events, myocardial infarction, stroke, pneumonia and thromboembolism). Restrictive transfusion strategies were associated with a statistically significant reduction in hospital mortality (RR 0.77, 95% CI 0.62 to 0.95) but not 30-day mortality (RR 0.85, 95% CI 0.70 to 1.03). The use of restrictive transfusion strategies did not reduce functional recovery, hospital or intensive care length of stay. The majority of patients randomised were included in good-quality trials, but some items of methodological quality were unclear. There are no trials in patients with acute coronary syndrome.

Authors' conclusions—The existing evidence supports the use of restrictive transfusion triggers in most patients, including those with pre-existing cardiovascular disease. As there are no trials, the effects of restrictive transfusion triggers in high-risk groups, such as acute coronary syndrome, need to be tested in further large clinical trials. In countries with inadequate screening of donor blood, the data may constitute a stronger basis for avoiding transfusion with allogeneic red cells.

Medical Subject Headings (MeSH)

*Practice Guidelines as Topic; Erythrocyte Transfusion [adverse effects; mortality; *standards]; Hematocrit [standards]; Hemoglobin A [analysis]; Randomized Controlled Trials as Topic; Reference Values; Transplantation, Autologous [standards]; Transplantation, Homologous [mortality; standards]

MeSH check words

Humans

BACKGROUND

Blood is an indispensable product in modern medical practice (Amin 2004). Red blood cells (RBC) are used to improve oxygen delivery to tissues in situations of haemorrhage and anaemia (Napolitano 2009). Red blood cell transfusion constitutes one of the mainstays of therapy in the management of anaemic patients and is one of the few treatments that

adequately restores tissue oxygenation when oxygen demand exceeds supply (Klein 2007; Wang 2010).

The risk and availability of red blood cell transfusion varies throughout the world. In most developed countries with well-regulated blood supplies, the safety of allogeneic red cell transfusion has improved significantly over the past 30 years. This has been primarily due to improvements in donor blood screening procedures and the implementation of more stringent quality control measures (Klein 2007). It has been estimated that the residual risk of transmission through transfusion of HIV, HCV and HBV in Canada is 1 per 7.8 million donations, 1 per 2.3 million donations and 1 per 153,000 donations respectively (O'Brien 2007). Globally, the estimated risks of infection per blood unit range from 1 per 100,000 to 1 per 400,000 for HBV, 1 per 1.6 million to 1 per 3.1 million for HCV, 1 per 1.4 million to 1 per 4.7 million for HIV, and 1 per 500,000 to 1 per 3.0 million for human T cell lymphotropic virus (Goodnough 2008). Data from seven developed countries from 2000 to 2005 showed the residual risk of transfusion-transmitted viral infections ranged from 0.22 to 2.48 per 1 million donations for HIV, 0.05 to 3.94 per 1 million donations for HCV and 1.51 to 9.78 per 1 million donations for HBV (Kitchen 2008). In the USA, the estimated risk per unit for HIV is 1:1,467,000 (Zou 2010), for HCV is 1:1,149,000 (Zou 2010) and for HBV is 1:282,000 to 357,000 (Zou 2009). In the USA, life-threatening reactions were also estimated to occur in 1: 139,908 patients transfused (Whitaker 2011).

In developing countries, the supply of blood is inadequate and may not be safe because it often is not tested for viral pathogens. Blood donations are not routinely tested in 39 countries for transfusion-transmissible infections including HIV, hepatitis B, hepatitis C and syphilis (WHO 2011). In 40 countries, less than 25% of the blood supply is collected from voluntary unpaid blood donors, with most coming from family or paid blood donors (WHO 2011). The prevalence of HIV in low-income countries is 2.3% of blood donations compared to 0.001% in high-income countries (WHO 2011).

Blood transfusion is expensive. In 2008, the mean payment for one unit of leukoreduced red blood cells in the United States was USD 223 (Whitaker 2011). However, if the costs of administration as well as the acquisition expenses of red blood cell transfusion are considered, the estimated cost derived from four US and European hospitals rises to USD 761 per unit (standard deviation +/− USD 294) (Shander 2010).

Description of the intervention

Historically, the widely accepted clinical standard was to transfuse patients when the haemoglobin level dropped below 10.0 g/dL or the haematocrit fell below 30%. This '10/30 rule' was first proposed by Adams and Lundy in 1942 and served as a RBC transfusion trigger for decades (Madjdpour 2005; Wang 2010). However, the 1988 National Institutes of Health Consensus Conference in the United States reported that the evidence did not support a single criterion for transfusion (NIH 1988). Since then, several published guidelines have advised against a single threshold for red cell transfusion, recommending that a range of haemoglobin values between 6.0 and 10.0 g/dL can be used, depending on the presence of serious co-morbidity (AAGBI 2008; ASA 2006; ASBT 2001; BCTMAG 2003; Napolitano 2009; NBUGI 2001).

Clinical trials evaluating transfusion thresholds usually compare two transfusion groups: 1) liberal transfusion where patients receive blood at a higher haemoglobin concentration, and 2) restrictive transfusion where patients receive blood at a lower haemoglobin concentration.

Why it is important to do this review

The purpose of the review was to find, appraise and summarise the data from high-quality trials that studied the clinical impact of varying thresholds for transfusion with red cells. We were particularly interested in whether the results of randomised controlled trials support the trend for increasingly restrictive red cell transfusion practices and if red cell transfusions can be withheld in some circumstances without harming patients. We have updated the review because two recent trials (Carson 2011; Hajjar 2010) were published, increasing the number of patients included in this review from 3746 to 6264.

OBJECTIVES

To examine the evidence for the effect of transfusion thresholds on the use of red cell transfusions and the evidence for any change in clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials with a concurrent control group. We included trials if the comparison groups were assigned on the basis of a clear transfusion 'trigger' or 'threshold', described as a haemoglobin or haematocrit level (with or without a specified level of haemodynamic instability) that had to be reached before a red cell transfusion was administered. Control group patients were required to be either transfused with allogeneic and/or autologous red blood cells at higher Hb or Hct levels (transfusion threshold) than the intervention group or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices.

Types of participants—We included trials of surgical or medical patients, involving adults and/or children. We excluded neonates.

Types of interventions—The intervention considered was the use of transfusion thresholds ('triggers') as a means of guiding allogeneic and/or autologous red blood cell transfusion.

Types of outcome measures

Primary outcomes

- The proportion of patients 'at risk' who were transfused with allogeneic and/or autologous red blood cells.

Secondary outcomes

- The amounts of allogeneic and autologous blood transfused.

- Morbidity (non-fatal myocardial infarction, cardiac events, pulmonary oedema, cerebral vascular accident, thromboembolism, renal failure, infection, haemorrhage, mental confusion), mortality, haematocrit levels (postoperative/discharge) and length of hospital stay (LOS). We expected the definitions of each of the morbidity events to vary between studies.

Search methods for identification of studies

We did not restrict our search for trials by date, language or publication status.

Electronic searches—The Cochrane Injuries Group Trials Search Co-ordinator conducted the latest search for trials and collated the results. We searched the following databases:

- the Cochrane Injuries Group's Specialised Register (searched 1 February 2011);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1);
- MEDLINE (Ovid) 1950 to January Week 3 2011;
- EMBASE (Ovid) 1980 to 2011 Week 04;
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to February 2011);
- ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to February 2011).

The search strategies are presented in Appendix 1.

Searching other resources—We contacted experts in the field to identify information relevant to the review. Where possible, we contacted authors of published studies for clarification of trial methodology and data. This was only possible where a contact address was reported in the published study. We searched the reference lists of relevant reviews and published papers as well as the reference lists of all included trials for further studies.

Data collection and analysis

Selection of studies—Two authors (JLC and PAC) independently screened the titles, abstracts, or both, of the search results and selected trials that met the previously defined inclusion criteria. We discussed inclusion of studies until consensus was reached; there were no disagreements on the inclusion of studies. We identified trials in which patients were randomised to a restrictive transfusion strategy (transfusion threshold and/or protocol), or to a control group which was randomised to a liberal transfusion strategy. JLC and PAC independently extracted study characteristics and outcomes using a data extraction form. The extraction form recorded information regarding: study type, methodology descriptions, the presence of a transfusion threshold, transfusion protocol, the type of surgery involved, clinical setting, treatment outcomes and general comments.

Data extraction and management—JLC and PAC performed data extraction on articles that met the inclusion criteria. JLC then entered data into Review Manager; data were checked by PAC. We contacted authors of trials to request missing data.

We used a data extraction form to record data on the following outcomes: the number of patients exposed to allogeneic blood, the amount of allogeneic blood transfused, the number of patients receiving any transfusion (allogeneic blood, autologous blood, or both). For trials involving surgical patients, we recorded the following outcomes: postoperative complications (infection, haemorrhage, non-fatal myocardial infarction, cardiac events, renal failure, stroke, thromboembolism, pulmonary oedema, mental confusion), mortality and length of hospital stay (LOS). We recorded data for blood loss and haemoglobin and haematocrit levels (on admission, pre-post transfusion and at discharge). We recorded information regarding demographics (age, sex), type of surgery or medical condition on the data extraction form. We extracted data for allogeneic blood transfusion if it was expressed as packed red blood cells (RBC). We documented information regarding the use of fresh frozen plasma (FFP) and/or platelets.

Assessment of risk of bias in included studies—The Cochrane Collaboration's tool for assessing risk of bias is described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

JLC and PAC assessed the following domains for each study:

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting;
- other potential sources of bias.

We completed a 'Risk of bias' table for each study, incorporating a description of the study's performance against each of the above domains and our overall judgement of the risk of bias for each entry as follows: 'Low', 'Unclear' (indicating unclear or unknown risk of bias) and 'High' risk of bias.

Measures of treatment effect—We calculated the risk ratio (RR) for allogeneic blood transfusion in the intervention group as compared with the control group and the corresponding 95% confidence intervals for each trial using the random-effects model (Der Simonian 1986). We adopted a similar approach to examine the other outcomes of transfusion. We also entered the mean number of units of red blood cells transfused to each group and the corresponding standard deviations. We used the mean difference (MD) and 95% confidence intervals (CI) to express the average reduction in the number of units of RBC administered to the intervention group, compared with the control.

Unit of analysis issues—The unit of analysis was the patient. We converted data expressed in millilitres (ml) for the volume of blood transfused to units of blood by dividing by 300.

Dealing with missing data—All analyses were on an intention-to-treat basis. We imputed no missing data.

Assessment of heterogeneity—There was significant clinical heterogeneity. The trials included surgical, medical and critical care patients. We pooled the data for all outcomes and presented data stratified by subgroups for the primary outcome only. The subgroups evaluated were allogeneic transfusion, autologous transfusion and clinical settings (cardiac surgery, orthopaedic surgery, vascular surgery, acute blood loss/trauma, cancer and critical care). We also examined the proportion of patients exposed to transfusion stratified by the transfusion threshold (difference ≥ 2 g/dL, < 2 g/dL), risk of bias and units of blood transfused.

We examined statistical heterogeneity using both the I^2 statistic and Chi^2 test. The I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when the $I^2 > 50\%$ (Higgins 2011). For the Chi^2 test, we used a P value of < 0.10 to indicate the presence of statistically significant heterogeneity.

Assessment of reporting biases—We examined funnel plots for evidence of publication bias. Although the small number of trials hampered funnel plot assessment, the outcome with the largest data set could be assessed for the presence of publication bias. The funnel plot for this outcome is presented in Figure 1.

Data synthesis—Due to the anticipated significant clinical heterogeneity of the trials, we analysed data using a random-effects model.

We performed all analyses using Review Manager software. We entered data on the numbers of patients exposed to allogeneic blood and the numbers of patients in each treatment group into Review Manager. We converted data in millilitres (ml) to units by dividing by 300. We converted studies reporting haematocrit to haemoglobin concentration by dividing by three.

Subgroup analysis and investigation of heterogeneity—We performed subgroup analyses to explore treatment effects by blood product (allogeneic versus autologous, units of blood transfused), clinical setting (cardiac surgery, orthopaedic surgery, vascular surgery, acute blood loss/trauma, cancer, critical care), transfusion threshold (difference ≥ 2 grams per decilitre and difference less than 2 grams per decilitre) and risk of bias.

Sensitivity analysis—We performed a sensitivity analysis to assess the effects of study allocation concealment on the results.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search—The original literature search conducted in 1999 identified 110 full-text articles. Of these 110 eligible studies, 99 were excluded from further assessment (transfusion audits and reviews n = 94; observational studies - cohort or case-control studies n = 5). We considered 11 full-text articles for review. Of these 11 studies one was excluded because the trigger was based on the level of HbS not the haemoglobin or haematocrit level.

We conducted an updated search in November 2004. No new trials were identified by this search.

An updated search conducted in 2009 identified an additional seven trials. A further search conducted in February 2011 identified an additional two trials.

Included studies—We identified and included 19 eligible studies in this review. Among the 19 included trials the clinical settings were variable. Eight studies took place within the context of surgery: cardiac, vascular or orthopaedic (Bracey 1999; Bush 1997; Carson 1998; Carson 2011; Foss 2009; Grover 2005; Hajjar 2010; Johnson 1992; Lotke 1999; So-Osman 2010). Five trials were in the context of acute blood loss and/or trauma (Blair 1986; Colomo 2008; Fortune 1987; Topley 1956; Zygun 2009), three trials involved patients in critical care units (Hebert 1995; Hebert 1999; Lacroix 2007) and one trial involved leukaemia patients undergoing chemotherapy or stem cell transplantation (Webert 2008).

There was considerable variation with regard to the restrictive transfusion strategies used. These varied from 7.0 to 9.0 g/dL, with two further trials specifying haematocrit values of 25% or 30% (equivalent to haemoglobin levels of around 8.0 and 10.0 g/dL respectively). The liberal transfusion triggers varied: 100% of ‘normal red cell volume’ (Topley 1956), two units of blood (immediately in one trial (Blair 1986), postoperatively in another (Lotke 1999)) irrespective of clinical state; transfusion sufficient to maintain haemoglobin levels at or above 12.0 g/dL (Webert 2008), 10.0 g/dL (Bush 1997; Carson 1998; Carson 2011; Foss 2009; Grover 2005; Hebert 1995; Hebert 1999); Hajjar 2010, 9.5 g/dL (Lacroix 2007) and 9.0 g/dL (Bracey 1999; Colomo 2008; Zygun 2009). Two trials specified the liberal triggers as haematocrit levels of 32% (Johnson 1992) and 40% (Fortune 1987). One trial compared a new uniform, restrictive transfusion policy with more liberal standard care (So-Osman 2010).

In these trials random allocation was at the level of the patient, not the clinician or clinical unit. Consequently, participating clinicians may have been responsible for patients in both arms of the trials. Ten trials included more than 100 patients. Only one trial included over 1000 patients (Carson 2011). A total of 6264 trial participants were included in this systematic review.

Excluded studies—One randomised controlled trial was confined to patients with sickle cell disease and was excluded as the trigger was based on the level of HbS, not the haemoglobin or haematocrit level (Vichinsky 1995).

Risk of bias in included studies

For further details regarding the performance of the studies against each domain, please see the 'Risk of bias' tables. A summary of the information in the tables is given below. Additionally, a visual summary of judgements about each methodological quality item for each included trial is shown in Figure 2 and Figure 3.

Sequence generation (selection bias)—We judged the risk of bias for this item to be low for nine trials, eight of which used computer randomisation and one which used a table of random numbers to generate the allocation sequence for the patients. One trial based the randomisation sequence on hospital record number and we judged it to be at high risk of bias, while the remaining nine trials presented insufficient information to assess the adequacy of sequence generation and we rated them as unclear.

Allocation—We judged the risk of bias for this item to be low for four trials which used central allocation. We rated 13 trials as unclear; seven used sealed envelopes, however, it was not clear if they were used with appropriate safeguards (e.g. sequentially numbered) to adequately conceal allocation. The other six rated as unclear did not present any information regarding allocation concealment. We rated two trials as being at high risk of bias for this domain.

Blinding—The nature of the intervention means that blinding of clinicians involved in the care and administration of blood transfusions would not have been feasible. The extent to which this could have biased the results is unclear, thus we have rated none of the studies as being at low risk of bias for this domain. However, blind outcome assessment was reported as being used in eight trials.

Incomplete outcome data—We rated 14 trials as being at low risk of bias for this domain as they either had no missing data or performed intention-to-treat analyses. A small number of exclusions were reported in the remaining five trials, although the extent to which this may have introduced bias is uncertain, thus we rated these trials as unclear.

Selective reporting—We could not find any evidence of reporting bias. Although we did not have access to the trial protocols for the majority of trials, the results for the primary and secondary outcomes, as described in the methods sections of each trial, were clearly and concisely reported. Trial protocols were available for the trials with which the authors had some degree of involvement (Carson 1998; Carson 2011; Hebert 1995; Hebert 1999; Lacroix 2007).

Other potential sources of bias—We identified no other sources of bias.

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Effects of interventions

Eighteen of the 19 trials presented data suitable for inclusion in the meta-analyses. One trial evaluated changes in brain tissue oxygen and other metabolic parameters (Zygun 2009).

Despite the heterogeneity in the methods and transfusion triggers reported in these randomised trials, it was possible to aggregate data from the following outcomes: exposure to red cell transfusion, exposure to red cell transfusion (allogeneic), average volume of red cells transfused in all patients, average volume of red cells transfused in transfused patients, haemoglobin concentration, cardiac events, myocardial infarction, pulmonary oedema, cerebrovascular accident, pneumonia, infection, mortality at 30 days, hospital mortality, overall length of hospital stay and intensive care unit length of hospital stay.

Proportion of patients transfused—Analysis 1.1

Data on the frequency of transfusions were available from 17 trials. On average, the implementation of a restrictive transfusion trigger reduced the risk of receiving a red cell transfusion by a relative 39% (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.52 to 0.72). Heterogeneity between these trials was statistically significant (Chi^2 = 238.95, df = 16 (P < 0.00001); I^2 = 93%).

The funnel plot displays an absence of smaller studies showing patients at elevated risk of receiving a transfusion with more restrictive transfusion triggers.

Quantity of red cells transfused—Analysis 1.7

The quantities of blood transfused were reported in eight trials. The use of a restrictive transfusion trigger resulted in an average saving of 1.19 units of red cells per transfused patient (mean difference (MD) −1.19, 95% CI −1.85 to −0.53). Heterogeneity between these trials was statistically significant (Chi^2 = 84.46, df = 7 (P < 0.00001); I^2 = 92%). One trial transfused autologous blood (Lotke 1999).

Haemoglobin or haematocrit concentration—Analysis 2.1

Postoperative haemoglobin or haematocrit levels were reported in 12 trials. In five trials the timing of measurement varied (the average measured over a number of days after hospitalisation (or operation)). In five trials a single value prior to discharge was recorded and in one trial a single value after the first transfusion was recorded. When we pooled data (without regard to timing, which was consistent within studies) patients assigned to a restrictive strategy had haemoglobin concentration on average 1.5% lower than patients assigned to a liberal transfusion strategy (MD −1.48, 95% CI −1.92 to −1.03). Heterogeneity between these trials was statistically significant (Chi^2 = 752.16, df = 11 (P < 0.00001); I^2 = 99%).

Mortality—Analysis 3.2; Analysis 3.5

Thirty-day mortality data were reported for 11 trials. There was no statistically significant difference in 30-day mortality between restrictive and liberal transfusion strategies (RR

0.85, 95% CI 0.70 to 1.03). Heterogeneity between these trials was not statistically significant (Chi^2 = 5.90, df = 9 (P = 0.75); I^2 = 0%). It should be noted that one study of patients in intensive care (Hebert 1999) contributed 52.0% and the study in patients with hip fracture (Carson 2011) contributed 23.4% of the weight in the meta-analysis of this outcome. Hospital mortality was 23% lower in patients in the restrictive compared to the liberal transfusion strategy (RR 0.77, 95% CI 0.62 to 0.95). Heterogeneity between the trials was not significant (Chi^2 = 1.35, df = 3 (P = 0.72); I^2 = 0%).

Hospital length of stay—Analysis 4.1

Eight trials reported data for length of hospital stay. These data indicated that the reduction in red blood cell transfusion was not associated with a prolongation of hospital stay (MD 0.11 days, 95% CI −0.16 to 0.38 days). Heterogeneity between these trials was not statistically significant (Chi^2 = 6.28, df = 7 (P = 0.51); I^2 = 0%). It is unclear if length of hospital stay included only patients who survived.

Functional recovery—Analysis 5.1; Analysis 5.2

Two trials reported functional outcomes in hip fracture patients (Carson 2011; Foss 2009). The functional measures were different in the trials and could not be combined. Death or inability to walk at 30 days (RR 1.05, 95% CI 0.95 to 1.15) or 60 days (RR 0.99, 95% CI 0.88 to 1.11) was not significant between transfusion strategies. No other measures of function were significantly different between transfusion strategies.

Cardiac events—Analysis 6.1

Seven trials reported data on cardiac events. The rates of cardiac events (myocardial infarction, cardiac arrhythmias, cardiac arrest, pulmonary oedema and angina) were not increased significantly by the use of restrictive transfusion strategies (RR 0.96, 95% CI 0.70 to 1.32). Heterogeneity between these trials was statistically significant (Chi^2= 16.87, df = 6 (P = 0.010); I^2 = 64%). It is likely that patients were counted in more than one category of this composite outcome.

Myocardial infarction—Analysis 6.2

Eight trials reported data on myocardial infarction (fatal and non-fatal). The use of a restrictive transfusion threshold did not appear to impact adversely on the rates of myocardial infarction (RR 0.88, 95% CI 0.38 to 2.04). There was no statistical heterogeneity between trials (Chi^2= 10.42, df = 7 (P = 0.17); I^2 = 33%).

Pulmonary oedema—Analysis 6.3

Five trials reported data for pulmonary oedema. There was no significant difference between the restrictive and liberal transfusion strategies (RR 0.72, 95% CI 0.31 to 1.70). Heterogeneity between the trials was significant (Chi^2 = 11.40, df = 4 (P = 0.02); I^2 = 65%).

Cerebrovascular accident - stroke—Analysis 6.4

Five trials reported on stroke. There was no significant difference between transfusion strategies (RR 0.84, 95% CI 0.47 to 1.49). Heterogeneity between the trials was not significant (Chi^2 = 2.61, df = 4 (P = 0.63); I^2 = 0%).

Pneumonia—Analysis 6.5

Five trials reported data for pneumonia. In contrast to overall infections; there was no significant difference between transfusion strategies (RR 0.93, 95% CI 0.76 to 1.15). Heterogeneity between these trials was not statistically significant (Chi^2= 2.51, df = 4 (P = 0.64); I^2 = 0%).

Infections—Analysis 6.8

Six trials reported data for infections. The rate of infections was decreased by 19% with the use of restrictive transfusion strategies although the results are not significant (RR 0.81, 95% CI 0.66 to 1.00). Heterogeneity between these trials was not statistically significant (Chi^2 = 5.70, df = 5 (P = 0.34); I^2 = 12%).

Other outcomes—A number of other potentially relevant clinical outcomes were reported in individual trials, including thromboembolism, multi-organ failure, mental confusion and delayed wound healing. Although there were no statistically significant differences between restrictive and liberal transfusion strategies for any of these outcomes, the overall event rates were low. Interestingly, one trial (Blair 1986) reported a decreased risk of re-bleeding in patients randomised to a restrictive transfusion strategy compared to patients randomised to a liberal transfusion strategy (RR 0.10, 95% CI 0.01 to 0.75). Where reported, heart rates, cardiac index and systemic vascular resistance also appeared to be unaffected (Bush 1997; Johnson 1992).

Sensitivity analyses—We performed a post hoc sensitivity analysis to explore the effects of the inclusion of data from the Webert 2008 trial in the pooled analyses. Webert 2008 explored whether a higher transfusion threshold would be beneficial for patients with acute leukaemia, unlike the other included studies which investigated the safety of a lower transfusion threshold. When we excluded data from Webert 2008 from the pooled analysis of blood transfusion exposure, the risk ratio was reduced slightly from 0.63 (95% CI 0.54 to 0.74) to 0.61 (95% CI 0.53 to 0.71). Heterogeneity between these trials remained statistically significant (Chi^2 = 96.82, df = 13, P < 0.00001; I^2 = 87%).

DISCUSSION

We identified 19 randomised controlled trials evaluating different red cell transfusion triggers carried out over a 55-year time period. These trials enrolled 6264 patients from divergent patient populations. The results of the meta-analyses indicated that, on average, restrictive transfusion strategies were associated with a reduction of more than one-third in the number of patients receiving blood, a red cell transfusion requirement that was approximately one unit lower, and a haemoglobin concentration (average postoperative) that

was around 1.5 g/dL lower than in the liberal transfusion group. However, such results need tempering against the significant heterogeneity of the trials assessed.

Sources of heterogeneity

For the primary outcome (the number of patients exposed to blood transfusion) we observed substantial heterogeneity. The variation was in terms of the size (but not the direction) of the treatment effect. The individual trials (with five exceptions: Bush 1997; Grover 2005; So-Osman 2010; Topley 1956; Webert 2008) found that a restrictive transfusion trigger statistically significantly reduced the probability of receiving a red cell transfusion, with the risk ratio estimates ranging from 0.21 to 0.96. However, some confidence intervals were non-overlapping. Heterogeneity might have been anticipated, as the clinical settings and the transfusion triggers differed between trials. In addition, the primary outcome in the meta-analysis, the decision to transfuse, is a practice variable and involves a degree of subjectivity. It cannot be argued that the treatment effect varied according to the rate of red cell transfusion in the control groups, as most patients (84%) in the liberal transfusion groups received red cell transfusions.

The level of the transfusion trigger between trials does not seem to account for the variation in treatment effect size; the relative risk appeared unrelated to it. However, the degree of difference within trials, between the transfusion triggers of the intervention and control groups, may account for some of the variation observed in the treatment effect size. The effect estimates for trials comparing well-defined transfusion rates that differed by 2.0 g/dL tended to be larger than the estimates for trials comparing thresholds differing by less than 2.0 g/dL. Although these apparent ‘associations’ may also be due to the play of chance, such observations warrant further discussion.

Two trials (Blair 1986; Lotke 1999) showed greater benefit (in favour of restrictive transfusion strategies) in reducing exposure to red cell transfusion, than any of the other trials. These two trials appeared to add considerably to the observed heterogeneity. In Blair 1986 the control group were routinely transfused (as dictated by the trial protocol) at least two units of blood within 24 hours of hospital admission, regardless of their Hb level and clinical state, whereas the intervention group were only transfused blood when their Hb concentration fell below 8.0 g/dL or they displayed signs of shock. For this trial (Blair 1986) the transfusion exposure rate for the intervention group was 19% compared to 100% for the control group. For the trial conducted by Lotke 1999 the control group received all of their preoperatively donated autologous (PAD) blood (2 units/patient) immediately after surgery (as dictated by the trial protocol) whereas the patients in the intervention group were not transfused their PAD blood unless their Hb concentration fell to less than 9.0 g/dL. For this trial (Lotke 1999) the transfusion exposure rate for the intervention group was 26% compared to 100% in the control group.

Five trials (Bush 1997; Grover 2005; So-Osman 2010; Topley 1956; Webert 2008) failed to show a statistically significant reduction in red cell transfusion rates. For Bush 1997 and Webert 2008 protocol violations may have impacted significantly on the rates of transfusion in the intervention groups. In Bush 1997, patients randomised to the intervention group were to be transfused allogeneic red cells, and in some instances autologous red cells, when their

Hb concentration fell below 9.0 g/dL; the control group were transfused when their Hb concentration fell below 10.0 g/dL. The authors of Bush 1997 conceded that not all the patients randomised to the restrictive transfusion strategy reached the transfusion threshold level of Hb < 9.0 g/dL because they either had minimal intra-operative blood loss or were excessively transfused by the anaesthetists or surgeons. The later may account for the relatively small difference in transfusion rates between the intervention and control groups (88% versus 80%, respectively). In Webert 2008, patients were allocated to receive RBC transfusion when their Hb level fell below 8.0 g/dL in the intervention group or 12.0 g/dL in the control. The trial authors note that a number of patients received transfusion before their assigned threshold had been reached; compliance with the assigned threshold was achieved only 64% of the time in the intervention and 70% of the time in the control group. This also may explain the similar transfusion rates observed in the two groups (90% and 94% for the restrictive and liberal groups, respectively). The trial by So-Osman 2010 compared a new age-dependent restrictive transfusion policy with the standard policy used in the three participating hospitals. Deviation from the assigned trigger was not found to be a problem, however differences in the transfusion threshold forming the standard policy of the hospitals may explain the lack of difference observed in transfusion rates (36% and 39% for intervention and control, respectively). The trial by Topley 1956 was designed so that one group of patients (‘under-transfused’ group) would have a red cell volume (RCV) of 70% to 80% of normal at the end of resuscitation, whilst the control group (‘adequately transfused’ group) would have a RCV of 100% of normal or over at the end of resuscitation. However, as reported, in practice these objectives were achieved with an accuracy of only ± 20%.

There is no evidence to suggest that clinical setting or adequacy of allocation concealment explains the variability in the effect estimates.

Adverse events and other outcomes

None of the outcomes evaluated, including mortality, cardiac morbidity, infections and length of hospital stay, appear to be adversely affected by the lower use of red cell transfusions. In contrast, the evidence raises the possibility of harm associated with liberal transfusion. In-hospital mortality and infections were 23% and 19% higher in patients receiving liberal transfusion, respectively. However, these findings should be interpreted cautiously. Mortality was not significantly different for the other time periods examined. The infection results were borderline significant and the risk of pneumonia was not elevated. Although very little heterogeneity was seen for the outcome variable mortality, the meta-analysis was dominated by two trials (Carson 2011; Hebert 1999) that contributed 75% of the statistical information.

These data are quite informative and support the recent move to more restrictive transfusion practices. Trials have now been performed in several settings where transfusion is widely used. Trials in adult and paediatric intensive care unit (ICU) patients confirm the safety of a 7.0 g/dL threshold in patients with severe acute illness. One trial in elderly hip fracture patients undergoing surgery and with extensive co-morbidity including underlying cardiovascular disease suggests that restrictive transfusion to 8.0 g/dL is safe as well. This

trial is also the first to demonstrate that liberal transfusion does not improve functional recovery.

Sources of bias

We performed extensive searches in an attempt to identify all eligible trials irrespective of publication status. Despite these efforts, inspection of the funnel plot (Figure 1) raises the possibility of publication bias or other small study biases affecting the exposure to blood transfusion outcome.

Our analyses demonstrate that only two trials in adults (Carson 2011; Hebert 1999) were adequately powered to evaluate the impact of different transfusion strategies on mortality, morbidity and function. Carson 2011 was the largest trial performed and included 2016 patients undergoing surgical repair for hip fracture. Hebert 1999 was the next largest study, involving 838 intensive care patients. Given this, the meta-analysis of mortality is dominated by studies in elderly surgical and intensive care patients and therefore it is uncertain if the results can be applied to other clinical settings. In paediatric intensive care unit patients there was no difference in new or progressive multiple-organ dysfunction syndrome (Lacroix 2007).

Several important clinical outcomes have not been adequately evaluated in the trials published to date. The studies evaluating myocardial infarction are too small to detect moderate differences and infection results are inconsistent. Observational data suggest that higher blood counts may be associated with less postoperative delirium (Weiskopf 2000).

This systematic review found new evidence of the safety of restrictive transfusion triggers in important subsets of patients with underlying cardiovascular disease (Carson 2011). Overall, the rates of cardiac events in this meta-analysis were not increased by the use of restrictive transfusion triggers; the trial was too small to detect small to moderate effects. However, evidence is still lacking in other important subsets of patients, including those with acute cardiovascular disease, renal failure and haematological disorders. Some guidelines recommend transfusion for symptoms or haemodynamic instability, rather than for a specific trigger haemoglobin level (AAGBI 2008; ASA 2006; ASBT 2001; Napolitano 2009; NBUGI 2001). This approach to transfusion was tested in a pilot study involving 84 patients (Carson 1998) and in a trial involving 2016 patients (Carson 2011) in which patients could be transfused with symptoms (cardiac chest pain, congestive heart failure and orthostatic hypotension or tachycardia unresponsive to adequate fluid challenge) or haemoglobin concentration less than 8.0 g/dL. These studies found no difference in functional recovery, mortality or morbidity in patients in the restrictive (symptomatic) transfusion group.

The results of these trials need to be viewed against six large observational studies that compared clinical outcomes at varying haemoglobin levels in transfused and non-transfused patients, and found conflicting results. In a study of 2202 patients undergoing coronary bypass surgery, the liberal transfusion group had a higher incidence of myocardial infarction than the conservative transfusion group (Spiess 1998). In a study of 8787 hip fracture patients, there was no difference in short or long-term mortality between patients transfused and not transfused down to a post-operative haemoglobin of 8.0 g/dL (Carson 1998). In a

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study of 4470 ICU patients, mortality was reduced in patients receiving transfusion of up to six units of blood (Hebert 1997). A retrospective study of 78,974 Medicare beneficiaries (Wu 2001) found that blood transfusion was associated with a lower short-term mortality rate among elderly patients with acute myocardial infarction if the haematocrit on admission was 30% or lower and that blood transfusion may be effective with a haematocrit as high as 33% on admission. A study of 310,311 patients 65 years or older who underwent major non-cardiac surgery found a 1.6% increase in 30-day postoperative mortality for each 1% decrease in preoperative haematocrit (Wu 2007). A study of 239,286 patients 65 years or older who underwent major non-cardiac surgery found intraoperative blood transfusion was associated with a reduction in mortality in patients with preoperative haematocrit levels of < 24% or in those with blood loss > 500 cc (Wu 2010). The main limitation of these observational studies is that there may be residual confounding by indication, despite the extensive statistical adjustment of the results. It is possible that differences in patient characteristics between transfused and non-transfused patients may not be identified, or adequately adjusted for. This point is emphasised by the fact that a randomised controlled trial (Hebert 1999) and an observational study (Hebert 1997) in intensive care patients, performed by the same group of investigators, came to opposite conclusions. Despite recent assertions to the contrary (Benson 2000; Concato 2000), we believe that adequately powered, rigorously performed, randomised clinical trials are the only way of overcoming these limitations.

A study presented at the Cochrane Colloquium in Lyon, France (9-13 October 2001) (Henry 2001a) highlighted the significant discrepancies in the results reported by randomised controlled trials compared to those reported by observational studies. This and other studies (Ioannidis 2001) have shown that disagreements in the magnitude of treatment effect between randomised controlled trials (RCTs) and observational studies are common. The authors of Henry 2001a analysed the data from studies of various interventions including: preoperative autologous donation (PAD), acute normovolemic haemodilution, cell salvage, laparoscopic cholecystectomy, hormone replacement therapy and antioxidant therapy. For PAD alone, the observational studies' (n = 41) estimate of treatment effect (risk ratio) for the number of patients exposed to allogeneic blood transfusion was 0.30 (95% confidence interval (CI) 0.26 to 0.35) compared to 0.39 (95% CI 0.27 to 0.57) for the RCTs (n = 7). For this intervention (PAD) there appears to be reasonable agreement between the results of the observational studies and the randomised controlled trials. However, the observational studies have appeared to over-estimate the magnitude of the treatment effect. Observational studies of the other interventions have tended to under-estimate the magnitude of treatment effect. Although the results obtained from well-conducted observational studies are extremely valuable, making inferences from observational data sets is problematic, as the sources of error and bias that afflict observational studies do not afflict randomised trials (Henry 2001a).

Conducting randomised clinical trials, where one intervention is a clinical policy regarding red cell transfusion, is demanding. Masking (blinding) the use of transfusion at the bedside is difficult to achieve unless study personnel are assigned to each patient, an expensive procedure. Outcomes that are determined by observers who are blind to the treatment group is probably the most rigorous approach that is practical. This approach was reported in only

eight of the trials reviewed here (Carson 1998; Carson 2011; Foss 2009; Grover 2005; Hajjar 2010; Johnson 1992; Lotke 1999; Webert 2008). Maintaining the integrity of the randomisation process becomes important if the trial is not to over-estimate the benefit of the intervention (Schulz 1995). Some studies in this review did not report the methods used to conceal the allocation sequence from the treating clinicians. Four trials (Carson 1998; Carson 2011; Lacroix 2007; Webert 2008) used a centralised allocation and four others (Bush 1997; Foss 2009; Hebert 1999; So-Osman 2010) used randomisation codes in sealed envelopes. The latter method has the potential to be unmasked, leading to the potential for selection bias in the inclusion of patients in the trials (Schulz 1995).

The transfusion policies reviewed here represent fairly small modifications to routine clinical practice. They are consistent with the recommendations of published clinical practice guidelines (AAGBI 2008; ASA 2006; ASBT 2001; BCTMAG 2003; Napolitano 2009; NBUGI 2001). The transfusion triggers (in terms of haemoglobin levels) were most often in the range of 8.0 to 9.0 g/dL, although values as low as 7.0 g/dL were assessed. In fact, the ‘restrictive’ transfusion triggers in some trials were equivalent to the ‘liberal triggers’ used in other trials. Nevertheless, the trials documented significant reductions in the rates of red cell transfusion and worthwhile blood conservation. These effects are similar to what has been documented in meta-analyses of trials of blood sparing techniques, such as cell salvage and anti-fibrinolytic drugs (Carless 2010; Henry 2011b). Adoption of a conservative transfusion threshold appears to be as effective as these technologies in avoiding the need for transfusion and is likely to cost less. In summary, a restrictive transfusion trigger reduces the risk of exposure to red blood cell transfusion and the total number of units transfused. The currently published evidence suggests that restrictive transfusion triggers do not adversely affect mortality, cardiac morbidity, function or length of hospital stay. For the present we recommend the use of a restrictive transfusion trigger, but suggest using caution in patients from high-risk groups such as acute coronary syndrome as there is currently no evidence from randomised controlled trials to guide treatment. In countries where there are serious doubts about the safety of donated blood, because of inadequate testing for viral pathogens, the existing data may constitute a stronger basis for avoiding red cell transfusion in many clinical settings.

AUTHORS’ CONCLUSIONS

Implications for practice

In patients who do not have acute coronary artery disease, blood transfusion can probably be withheld in the presence of haemoglobin levels as low as 7.0 g/dL to 8.0 g/dL as long as there is no notable bleeding. The benefits of minimising allogeneic red cell transfusion are likely to be greatest where there is doubt about the safety of the blood supply.

Implications for research

Future trials of transfusion ‘triggers’ should include patients with acute coronary syndrome, elderly patients recovering from acute illness, patients with gastrointestinal bleeding, coagulopathy or haemorrhagic shock, and patients with traumatic brain injury. Trials are

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also needed that evaluate lower haemoglobin concentrations such as 6.0 g/dL. Trials should be large enough to measure the impact that lower thresholds have on clinical outcomes.

Acknowledgments

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SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NSW Ministerial Advisory Committee on Quality in Health Care, Australia.
- NSW Health Department, Australia.

Appendix 1. Search strategy

Cochrane Injuries Group's Specialised Register (searched 1 February 2011)

(Blood or "Red blood cell" or "Red blood cells" or RBC) and (therap* or transfus*) and (polic* or practice or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard* or restrict* or liberal* or management or program*)

Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 1)

#1	MeSH descriptor Blood Transfusion, this term only with qualifiers: MT,ST
#2	transfus* near5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)
#3	(Red blood cell* or RBC) near5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*) and (therap* or transfus*)
#4	(H?emoglobin or h?emocrit or HB or HCT) near5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)
#5	transfus* near5 (restrict* or liberal*)
#6	(blood transfus*) near3 (management or program*)
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

MEDLINE (Ovid) 1948 to January Week 3 2011

1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.
3. 1 or 2
4. exp Reference Standards/
5. standards.fs.
6. methods.fs.
7. 4 or 5 or 6
8. 3 and 7
9. (transfus* adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
10. ((Red blood cell* or RBC) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
11. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
12. (transfus* adj5 (restrict* or liberal*)).mp.
13. ((blood or transfus*) adj3 (management or program*)).mp.
14. 8 or 9 or 10 or 11 or 12 or 13
15. randomi?ed.ab,ti.
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. placebo.ab.
19. clinical trials as topic.sh.
20. randomly.ab.
21. trial.ti.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. (animals not (humans and animals)).sh.
24. 22 not 23
25. 24 and 14

EMBASE (Ovid) 1980 to 2011 Week 04

1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.

3. 1 or 2
4. exp standard/
5. 3 and 4
6. (transfus* adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
7. ((Red blood cell* or RBC) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
8. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic*or practic* or protocol* or trigger* or threshold*or indicator* or strateg* or criteri* or standard*)).mp.
9. (transfus* adj5 (restrict* or liberal*)).mp.
10. ((blood or transfus*) adj3 (management or program*)).mp.
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp Randomized Controlled Trial/
13. exp controlled clinical trial/
14. randomi?ed.ab,ti.
15. placebo.ab.
16. *Clinical Trial/
17. randomly.ab.
18. trial.ti.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp animal/not (exp human/and exp animal/)
21. 19 not 20
22. 11 and 21

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to February 2011) and ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to February 2011)

#1 TS=((Blood or “Red blood cell” or “Red blood cells” or RBC or Hemoglobin* or haemoglobin* or haemocrit or hemocrit or HB or HCT) SAME transfus*)

#2 TS=(polic* or practice or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard* or restrict* or liberal* or management or program*)

#3 #1 and #2

#4 TS=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)

#5 TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))

#6 #2 or #3

#7 #3 and #6

#8 Topic=(human*)

#9 #7 and #8

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blair 1986

Methods	Randomised controlled trial
Participants	50 consecutive patients with severe upper gastrointestinal haemorrhage were randomised to 1 of 2 groups: • Liberal group: n = 24; mean (SD) age = 64 (17.6) years • Restrictive group: n = 26; mean (SD) age = 60 (17.8) years
Interventions	• Liberal group received at least 2 units of red blood cells immediately at admission and during their first 24 hours in hospital. • Restrictive group were not transfused red blood cells unless the Hb was less than 8.0 g/dL or shock persisted after initial resuscitation with Haemaccel
Outcomes	***Outcomes reported:*** blood usage (units), re-bleeding, mortality, clotting times, Hct on admission/discharge, kaolin cephalin clotting time after 24 hours, impedance clotting time after 24 hours
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data

Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Bracey 1999

Methods	Randomised controlled trial
Participants	428 consecutive patients undergoing elective primary coronary artery bypass graft surgery were randomly assigned to 1 of 2 groups: • Liberal group: n = 212; M/F = 82/18; mean (SD) age = 61 (11) years • Restrictive group: n = 216; M/F = 83/17; mean (SD) age = 62 (11) years
Interventions	• Liberal group received transfusions on the instructions of their individual physicians, who considered the clinical assessment of the patient and the institutional guidelines, which propose a Hb level < 9.0 g/dL as the postoperative threshold for RBC transfusion • Restrictive group received a RBC transfusion in the postoperative period at a Hb level < 8.0 g/dL
Outcomes	***Outcomes reported:*** mortality, length of hospital stay, blood usage (units), blood loss, complications, infection rates, cardiac events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Patients were randomly assigned on the basis of the last digit of their medical record number
Allocation concealment (selection bias)	High risk	Inadequately concealed (record number)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used. A small number of exclusions were reported
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Bush 1997

Methods	Randomised controlled trial
Participants	99 patients undergoing elective aortic or infrainguinal arterial reconstruction were randomised to 1 of 2 groups: • Liberal group: n = 49; M/F = 41/8; mean (SD) age = 64 (11) years

	• Restrictive group: n = 50; M/F = 32/18; mean (SD) age = 66 (10) years
Interventions	• Liberal group had their Hb concentrations maintained at or above 10.0 g/dL • Restrictive group were transfused only when their Hb concentration fell below 9. 0 g/dL
Outcomes	***Outcomes reported:*** 30-day mortality, length of ICU stay, length of hospital stay, blood use (units), postoperative blood loss, cardiac events, Hct/Hb on admission
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were chosen at random for patient assignment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Both surgeons and anaesthesiologists were informed as to the group of randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be complete
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Carson 1998

Methods	Randomised controlled trial
Participants	84 hip fracture patients undergoing surgical repair who had postoperative Hb levels < 10.0 g/dL were randomly assigned to 1 of 2 groups: • Liberal group: n = 42; M/F = 9/33; mean (SD) age = 81.3 (8.1) years • Restrictive group: n = 42; M/F = 11/31; mean (SD) age = 83.3 (10.8) years
Interventions	• Liberal group received 1 unit of packed RBC at the time of random assignment and as much blood as necessary to keep the Hb level above 10.0 g/dL • Restrictive group received a RBC transfusion for symptoms of anaemia or for a Hb level that dropped below 8.0 g/dL
Outcomes	***Outcomes reported:*** mortality, length of hospital stay, blood usage (units), complications, pneumonia, stroke, thromboembolism
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedules were stratified by clinical site and cardiovascular disease state. The randomisation was designed in blocks of 2 to 8 patients to avoid imbalance within a site

Allocation concealment (selection bias)	Low risk	Study personnel at the clinical sites randomly assigned patients by contacting the data co-ordinating centre's 24-hour automated telephone service
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	-
Other bias	Low risk	-

Carson 2011

Methods	Randomised, unblinded, parallel, 2-group multicentre trial
Participants	Patients 50 years or older, who are undergoing surgical repair of a hip fracture, with Hb concentrations below 10.0 g/dL within 3 days after surgery and who have clinical evidence for cardiovascular disease or cardiovascular risk factors Sample size = 2016
Interventions	• Liberal group - receive packed RBC when haemoglobin level dropped below 10.0 g/dL • Restrictive ('symptomatic strategy') group - receive transfusion if develop symptoms of anaemia or if Hb falls below 8.0 g/dL
Outcomes	Primary outcome is inability to walk 10 feet (or across a room) without human assistance or death prior to closure of the window for the 60-day, 30 and 60-day mortality. Other outcomes are Hb concentration, acute coronary syndrome (ACS), in-hospital myocardial infarction, unstable angina or death, disposition on discharge, survival, functional measures, fatigue/energy, readmission to hospital, pneumonia, wound infection, thromboembolism, stroke or transient ischaemic attack
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data Co-ordinating Center staff prepared randomisation schedules for each site using randomly ordered block sizes of 2, 4, 6 or 8
Allocation concealment (selection bias)	Low risk	Used an automated telephone randomisation system
Blinding (performance bias and detection bias) All outcomes	Unclear risk	After random allocation, clinical site staff, clinicians and patients were not blinded to treatment assignment. Primary and secondary outcomes were assessed blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	-
Other bias	Low risk	-

Colomo 2008

Methods	Randomised controlled trial
Participants	214 patients with acute gastrointestinal bleeding and cirrhosis were randomly allocated to 1 of 2 groups: • Liberal group: n = 105 • Restrictive group: n = 109 NB: no demographic information was presented, although stated that baseline characteristics were similar in the 2 groups
Interventions	• Liberal group received packed RBC when Hb level dropped below 9.0 g/dL (to maintain Hb concentration at 9.0 to 10.0 g/dL) • Restrictive group received packed RBC when Hb level dropped below 7.0 g/dL (to maintain Hb concentration at 7.0 to 8.0 g/dL)
Outcomes	***Outcomes reported:*** mortality, therapeutic failures, transfusion, Hb concentration, side effects
Notes	Conference abstract

Risk Of Bias

Bias	Author' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information presented to permit judgement of 'Yes' or 'No'
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Fortune 1987

Methods	Randomised controlled trial
Participants	25 patients were studied prospectively following acute injury and haemorrhage. These patients were randomised to 1 of 2 groups: • Liberal group: n = 13; mean age = 46.9 years • Restrictive group: n = 12; mean age = 46.5 years
Interventions	• Liberal group had their Hct brought up to 40% slowly over a period of several hours by the infusion of packed red cells • Restrictive group had their Hct maintained close to 30% by the appropriate administration of packed red cells NB: all patients had sustained a Class III or Class IV haemorrhage and had clinical signs of shock (systolic blood pressure < 90 torr, heart rate >100 bpm or urine output < 20 ml/hr) before entry into the study. Patients were resuscitated according to the clinical protocol of the centre first using crystalloid to re-establish organ perfusion and haemodynamic stability and then giving sufficient

	packed red cells to achieve a Hct close to 30%. Patients were studied twice a day for 3 days after the period of haemorrhagic shock
Outcomes	***Outcomes reported:*** RBC consumption (units), cardiopulmonary parameters: pulmonary capillary wedge pressure (PCWP), intrapulmonary shunt, tissue oxygenation/perfusion, oxygen consumption/delivery, arterial and venous O_2 saturations, arterial and venous O_2 contents, cardiac index (CI), heart rate, systemic vascular resistance, left ventricular stroke work index
Notes	

Risk Of Bias

Bias	Author' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to have been complete
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Foss 2009

Methods	
Participants	120 hip fracture patients were randomly allocated to 1 of 2 groups: • Liberal group: n = 60; M/F = 14/46; mean (SD) age = 81 (6.8) years • Restrictive group: n = 60; M/F = 14/46; mean (SD) age = 81 (7.3) years
Interventions	• Liberal group received packed RBC when Hb level dropped below 10.0 g/dL • Restrictive group received packed RBC when Hb level dropped below 8.0 g/dL
Outcomes	***Outcomes reported:*** ambulatory capacity, mortality, length of stay, cardiac complications, infectious complications
Notes	

Risk Of Bias

Bias	Author' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported as being double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Grover 2005

Methods	Randomised controlled trial
Participants	260 patients undergoing elective lower limb joint replacement surgery were randomly allocated to 1 of 2 groups: • Liberal group: n = 109; M/F = 55/54; mean (SD) age = 71.5 (7.6) years • Restrictive group: n = 109; M/F = 48/61; mean (SD) age = 70.7 (7.1) years
Interventions	• Liberal group received packed RBC when Hb level dropped below 10.0 g/dL, and Hb concentration maintained between 10.0 to 12.0 g/dL • Restrictive group received packed RBC when Hb level dropped below 8.0 g/dL and Hb concentration maintained between 8.0 to 9.5 g/dL
Outcomes	***Outcomes reported:*** ischaemic load, blood load, Hb concentration, number of units transfused, length of hospital stay, adverse events, new infections requiring antibiotic therapy
Notes	

Risk Of Bias

Bias	**Author' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Anaesthetists and surgical team responsible for treatment were aware of allocation. Outcome assessment was blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of a recruited 260 patients, outcome data presented for 218. Missing 42 did not have analysable tape recordings
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Hajjar 2010

Methods	Randomised clinical trial
Participants	502 adult patients who underwent cardiac surgery with cardiopulmonary bypass • Liberal group: n = 257; M/F = 161/92; mean (SD) age 60.7 (12.5) years • Restrictive group: n = 255; M/F = 149/100; mean (SD) age 58.6 (12.5)
Interventions	• Liberal group were transfused RBC if the haematocrit was less than 30% at any time from the start of surgery until discharge from the ICU • Restrictive group were transfused if haematocrit values were less than 24%
Outcomes	**Outcomes reported:** primary outcome composite endpoint that included 30-day all-cause mortality and severe morbidity (cardiogenic shock, ARDS or acute renal injury requiring dialysis or haemofiltration. Respiratory, cardiac, neurologic and infectious complications; inflammatory complications; bleeding; ICU and hospital lengths of stay, RBC transfusions.)
Notes	

Risk Of Bias

Bias	**Author' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random-number table prepared by chief statistician
Allocation concealment (selection bias)	Unclear risk	Opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Patient and outcome assessors were blinded; clinicians were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat. Complete follow-up.
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Hebert 1995

Methods	Randomised controlled trial
Participants	69 normovolaemic critically ill patients admitted to 1 of 5 tertiary level intensive care units with Hb values < 9.0 g/dL within 72 hours of admission were randomly assigned to 1 of 2 groups: • Liberal group: n = 36; M/F = 19/17; mean (SD) age = 59 (21) years • Restrictive group: n = 33; M/F = 14/19; mean (SD) age = 58 (15) years
Interventions	• Liberal group were transfused RBC if the Hb level fell to between 10.0 to 10.5 g/dL. Hb level maintained between 10.0 to 12.0 g/dL. • Restrictive group were transfused RBC if the Hb level fell to between 7.0 to 7.5 g/dL. Hb level was maintained between 7.0 to 9.0 g/dL.

Outcomes	***Outcomes reported:*** mortality, length of hospital stay, length of ICU stay, blood usage (units), complications, Hb levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were assigned to 1 of 2 groups by consecutive allocation from a random listing stratified by centre and disease severity
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias All outcomes	Unclear risk	"Blinding of treatment allocation was not feasible"
Incomplete outcome data (attrition bias All outcomes	Low risk	Intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	-
Other bias	Low risk	-

Hebert 1999

Methods	Randomised controlled trial
Participants	838 critically ill patients with euvolemia after initial treatment who had Hb concentrations <9.0 g/dL within 72 hours after admission to the intensive care unit were randomly assigned to 1 of 2 groups: • Liberal group: n = 420; M/F = 255/165; mean (SD) age = 58.1 (18.3) years • Restrictive group: n = 418; M/F = 269/149; mean (SD) age = 57.1 (18.1) years
Interventions	• Liberal group were transfused RBC when the Hb concentration fell below 10.0 g/dL. The Hb concentration was maintained between 10.0 to 12.0 g/dL. • Restrictive group were transfused RBC if the Hb concentration dropped below 7. 0 g/dL. The Hb concentration was maintained between 7.0 to 9.0 g/dL.
Outcomes	***Outcomes reported:*** mortality, length of hospital stay, length of ICU stay, blood usage (units), complications, infection rates, cardiac events, pulmonary oedema, pneumonia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random order
Allocation concealment (selection bias)	Unclear risk	Sealed, opaque envelopes prepared by the data-coordinating centre and distributed to each participating institution where they were opened up sequentially to determine the patients treatment assignment. The envelopes were returned periodically to the co-ordinating centre for auditing

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"It was not feasible to mask the assigned transfusion strategy from health care providers"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	-
Other bias	Low risk	-

Johnson 1992

Methods	Randomised controlled trial
Participants	39 autologous blood donors undergoing elective myocardial revascularisation were randomised to 1 of 2 groups: • Liberal group: n = 18; M/F = 16/2; mean (SD) age = 60.5 (6.9) years • Restrictive group: n = 20; M = 20; mean (SD) age = 58.2 (7.5) years
Interventions	• Liberal group received blood to achieve a Hct value of 32% • Restrictive (conservative) group received transfusions for a Hct value less than 25% NB: operative management included sequestration of 1 or more units of fresh autologous blood in patients with a Hct value greater than 35% who were haemodynamically stable after anaesthetic induction. Red cell conservation was practised through salvage of oxygenator contents and reinfusion of postoperatively shed mediastinal blood. On the 5th postoperative day all patients were asked to complete an exercise treadmill test. A second test was performed the following day
Outcomes	***Outcomes reported:*** cardiac events, complications, postoperative blood loss, blood use (total units), allogeneic blood use (units), autologous blood use (units), all product blood use (units), number of patients receiving transfusions, mean cardiac index, mean systemic resistance, exercise capacity, Hct levels, length of ICU stay, length of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised with the aid of a table of random numbers and an odd-even designation
Allocation concealment (selection bias)	High risk	Inadequately concealed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Surgeons and anaesthesiologists were blinded as to the group of randomisation until the patient reached the intensive care unit (ICU)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A small number of exclusions were reported
Selective reporting (reporting bias)	Unclear risk	-

Other bias	Low risk	-

Lacroix 2007

Methods	Randomised controlled trial
Participants	637 stable, critically ill children with Hb concentrations below 9.5 g/dL within 7 days after admission to an ICU were randomly allocated to 1 of 2 groups: • Liberal group: n = 317; M/F = 191/126; mean (SD) age = 39.6 (51.9) months • Restrictive group: n = 320; M/F = 190/130; mean (SD) age = 35.8 (46.2) months
Interventions	• Liberal group were transfused RBC when the Hb concentration fell below 9.5 g/dL, with a target range of 11.0 to 12.0 g/dL • Restrictive group were transfused RBC ifthe Hb concentration dropped below 7. 0 g/dL, with a target range of 8.5 to 9.5 g/dL
Outcomes	***Outcomes reported:*** 28-day mortality, sepsis, transfusion reactions, infections, length of stay
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Internet-based, central allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Clinical staff and parents of the patients were aware of the assignments to study groups, but the statistician and members of the data and safety monitoring committee were unaware of the assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	-
Other bias	Low risk	-

Lotke 1999

Methods	Randomised controlled trial
Participants	152 patients undergoing primary total knee arthroplasty (TKA) were randomly assigned to 1 of 2 groups: • Liberal group: n = 65; M/F = 19/46; mean age = 69.7 years • Restrictive group: n = 62; M/F = 20/42; mean age = 68.7 years
Interventions	• Liberal group were transfused autologous blood immediately after TKA, beginning in the recovery room postoperatively

- Restrictive group were transfused autologous blood when the Hb level had fallen to < 9.0 g/dL

Outcomes	***Outcomes reported:*** complications, cardiac events, Hb levels, blood usage (units), mental confusion, lethargy, orthostatic hypotension, number of patients transfused
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Assessments were made by a person blind to the group to which the patient was assigned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears to have been complete
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

So-Osman 2010

Methods	Randomised controlled trial
Participants	619, patients undergoing elective orthopaedic hip/knee replacement surgery were randomised to 1 of 2wo groups: • Liberal (standard care) group: n = 304; M/F = 118/186; mean (SD) age = 70.3 (9. 7) years • Restrictive (new transfusion policy) group: n = 299; M/F = 84/215; mean (SD) age = 70.7 (10.2) years
Interventions	• Liberal group received standard care • Restrictive group were treated using a 'new transfusion policy'
Outcomes	***Outcomes reported:*** red blood cell usage, length of hospital stay, Hb levels, mobilisation delay, postoperative complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Clinicians caring for the patients were aware of allocation status, however, the study investigators were not

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis was not performed, although unclear if this would have biased the results
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Topley 1956

Methods	Randomised controlled trial
Participants	22 trauma patients were randomly allocated to 1 of 2 groups: • Liberal group: n = 10 • Restrictive group: n = 12 NB: no demographic data were reported
Interventions	• Liberal group: the aim was to achieve 100% or more of the red cell volume at the end of resuscitation • Restrictive group: an attempt was made to leave the red cell volume at the end of resuscitation at 70% to 80% of normal
Outcomes	***Outcomes reported:*** blood usage (units), blood loss, wound healing, elevated temperature, number of patients transfused, Hb levels
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	When the patient was considered eligible for the trial, they were placed in a severity grade and an envelope opened to decide which transfusion schedule was to be used
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be complete
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Webert 2008

Methods	Randomised controlled trial
Participants	60 adult patients with acute leukaemia were randomly allocated to 1 of 2 groups: • Liberal group: n = 31; M/F = 14/17; mean (SD) age = 45.3 (16.8) years • Restrictive group: n = 29; M/F = 1811; mean (SD) age = 50.8 (15.3) years

Interventions	• Liberal group were transfused 2 units of RBC when the Hb concentration fell below 12.0 g/dL • Restrictive group were transfused 2 units of RBC if the Hb concentration dropped below 8.0 g/dL, with a target range of85 to 95 g/dL
Outcomes	***Outcomes reported:*** transfusions, bleeding risk
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence generation
Allocation concealment (selection bias)	Low risk	Internet-based, central allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Single-blinded" - blind outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Zygun 2009

Methods	Randomised controlled trial
Participants	30 patients with severe traumatic brain injury were randomly allocated to 1 of 3 groups: • Liberal group 1: n = 10 • Liberal group 2: n = 10 • Restrictive group: n = 10 NB: Mean (SD) age = 39 (15) years, 70% of trial participants were male
Interventions	• Liberal group 1 were transfused 2 units of RBC when the Hb concentration fell below 9.0 g/dL • Liberal group 2 were transfused 2 units of RBC when the Hb concentration fell below 10.0 g/dL • Restrictive group were transfused 2 units of RBC if the Hb concentration dropped below 8.0 g/dL
Outcomes	***Outcomes reported:*** change in brain tissue oxygen, brain pH, mortality
Notes	Additional data were obtained from lead trialist for inclusion in the meta-analysis. Data from liberal groups 1 and 2 combined for analysis

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Low risk	-

Hb = haemoglobin

Hct = haematocrit

ICU = intensive care unit

PCWP = pulmonary capillary wedge pressure

RBC = red blood cells

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Vichinsky 1995	Intervention not relevant

Characteristics of studies awaiting assessment *[ordered by study ID]*

Cooper 2011

Methods	Randomised clinical trial
Participants	Patients with acute myocardial infarction and haematocrit less than 30% Sample size = 45 patients
Interventions	Liberal transfusion: transfuse when haematocrit < 30% to maintain 30% to 33%) Conservative transfusion: transfuse when haematocrit < 24% to maintain 24% to 27%
Outcomes	The primary clinical safety measurement of in-hospital death, recurrent myocardial infarction, or new or worsening congestive heart failure
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

MINT

Trial name or title	Myocardial ischemia and transfusion
Methods	Randomised, single-blinded, parallel trial
Participants	Anaemic patients with acute coronary syndrome, aged 18 years or over Sample size =110
Interventions	• Liberal group - receive 1 unit of packed RBC following randomisation and received enough blood to raise Hb concentration above 10 g/dL, during hospitalisation for up to 30 days • Restrictive group - receive transfusion if develop symptoms of anaemia or if Hb falls below 8.0 g/dL
Outcomes	Trial performance and feasibility, Hb concentration, mortality or myocardial ischaemia, unscheduled hospital admission, stroke, congestive hear failure, stent thrombosis, deep vein thrombosis, pulmonary embolism, pneumonia, blood stream infection
Starting date	September 2009
Contact information	Jeffrey Carson (carson@umdnj.edu)
Notes	

TITRe 2

Trial name or title	A multi-centre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and healthcare resources use following cardiac surgery
Methods	Multicentre randomised controlled trial
Participants	Patients aged 16 years and over undergoing cardiac surgery
Interventions	• Liberal group - receive packed RBC if Hb concentration falls below 9 g/dL, objective is to maintain Hb above 9 g/dL • Restrictive group - receive packed RBC if Hb concentration falls below 7.5 g/dL, objective is to maintain Hb above 7.5 g/dL
Outcomes	Infectious events, ischaemic events, units of RBC transfused, duration of hospital stay, all-cause mortality, resource use
Starting date	December 2008
Contact information	
Notes	

Hb = haemoglobin

RBC = red blood cells

DATA AND ANALYSES

Comparison 1
Blood transfusions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients exposed to blood transfusion (all studies)	17	6125	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.52, 0.72]
2 Patients exposed to allogeneic blood transfusion	10	4146	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.46, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Patients exposed to autologous blood transfusion	2	165	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.12, 1.82]
4 Patients exposed to blood transfusion (by clinical setting)	17	6127	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.52, 0.72]
4.1 Cardiac surgery	3	968	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.58, 0.78]
4.2 Orthopaedic surgery	6	3170	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.37, 0.75]
4.3 Vascular	1	99	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.08]
4.4 Acute blood loss/ trauma	3	286	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.30, 0.89]
4.5 Cancer	1	60	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.12]
4.6 Critical care	3	1544	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.75]
5 Patients exposed to blood transfusion (by transfusion threshold)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Difference ≥ 2 g/dL	10	4758	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.72]
5.2 Difference < 2 g/dL	2	527	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.07]
6 Patients exposed to blood transfusion (by allocation concealment)	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Low risk of bias	4	2797	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.37, 0.80]
6.2 Unclear risk ofbias	11	2862	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.54, 0.74]
6.3 High risk of bias	2	466	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
7 Units of blood transfused	8	2715	Mean Difference (IV, Random, 95% CI)	−1.19 [−1.85, −0.53]
8 Units of blood transfused in those transfused	8	1555	Mean Difference (IV, Random, 95% CI)	−0.75 [−1.30, −0.20]

Comparison 2
Haemoglobin concentration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Haemoglobin concentration	12	5302	Mean Difference (IV, Random, 95% CI)	−1.48 [−1.92, −1.03]

Comparison 3
Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ≤14-day mortality	2	821	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.06, 2.96]
2 30-day mortality	11	4979	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.03]
3 60-day mortality	3	2938	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.72, 1.06]
4 120-day mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Hospital mortality	5	3411	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.62, 0.95]
6 ICU mortality	3	736	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.59, 2.23]
7 Mortality (unspecified follow-up period)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 4
Length of stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital length of stay	8	4226	Mean Difference (IV, Random, 95% CI)	0.11 [−0.16, 0.38]
2 ICU length of stay	5	2114	Mean Difference (IV, Random, 95% CI)	−0.15 [−0.66, 0.37]

Comparison 5
Function and fatigue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Inability to walk or death at 30 days	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Inability to walk or death at 60 days	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Lower extremity physical activities of daily living at 30 days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Lower extremity physical activities of daily living at 60 days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5 Instrumental activities of daily living at 30 days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6 Instrumental activities of daily living at 60 days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7 Energy/fatigue at 30 days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Energy/fatigue at 60 days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 6
Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiac events	7	4048	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.32]
2 Myocardial infarction	8	3884	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.38, 2.04]
3 Pulmonary oedema	5	3649	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.70]
4 Cerebrovascular accident (CVA) - stroke	5	2760	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.47, 1.49]
5 Pneumonia	5	3695	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.15]
6 Thromboembolism	3	2220	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.32, 1.59]
7 Rebleeding	2	552	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.03, 4.99]
8 Infection	6	4306	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 1.00]
9 Renal failure	3	1567	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.56, 2.18]
10 Mental confusion	2	247	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.63, 5.44]

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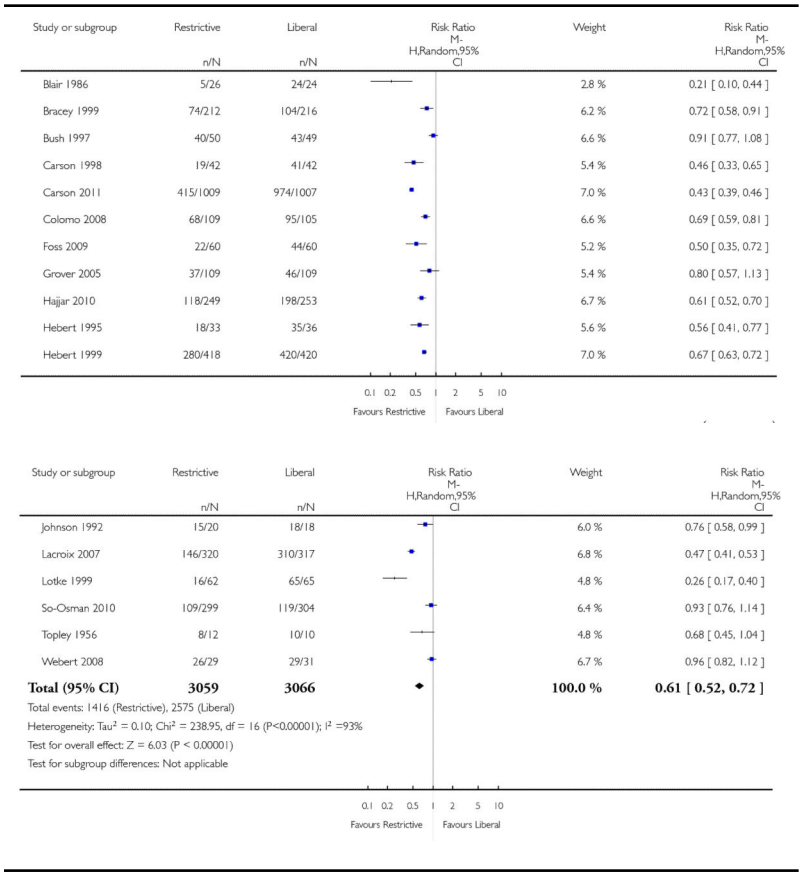
Analysis 1.1

Comparison 1 Blood transfusions, Outcome 1 Patients exposed to blood transfusion (all studies)

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

Comparison: 1 Blood transfusions

Outcome: 1 Patients exposed to blood transfusion (all studies)



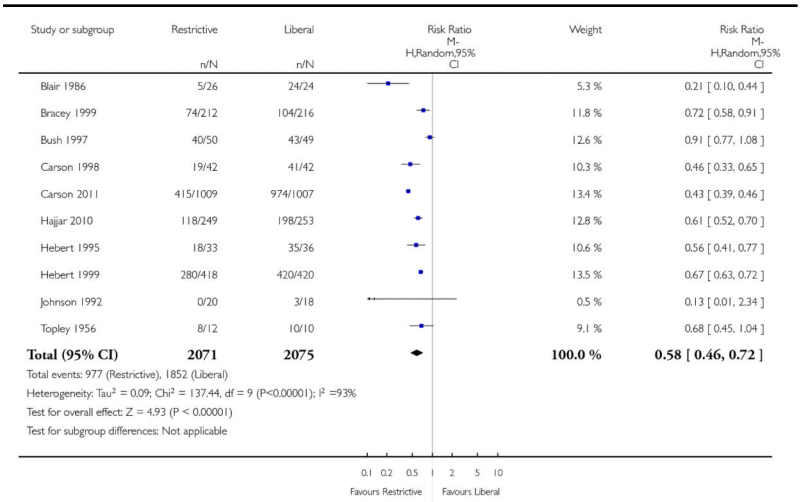
Analysis 1.2

Comparison 1 Blood transfusions, Outcome 2 Patients exposed to allogeneic blood transfusion

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

Comparison: 1 Blood transfusions

Outcome: 2 Patients exposed to allogeneic blood transfusion



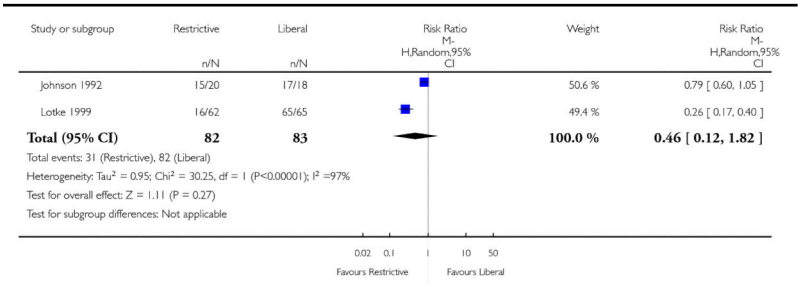
Analysis 1.3

Comparison 1 Blood transfusions, Outcome 3 Patients exposed to autologous blood transfusion

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

Comparison: 1 Blood transfusions

Outcome: 3 Patients exposed to autologous blood transfusion



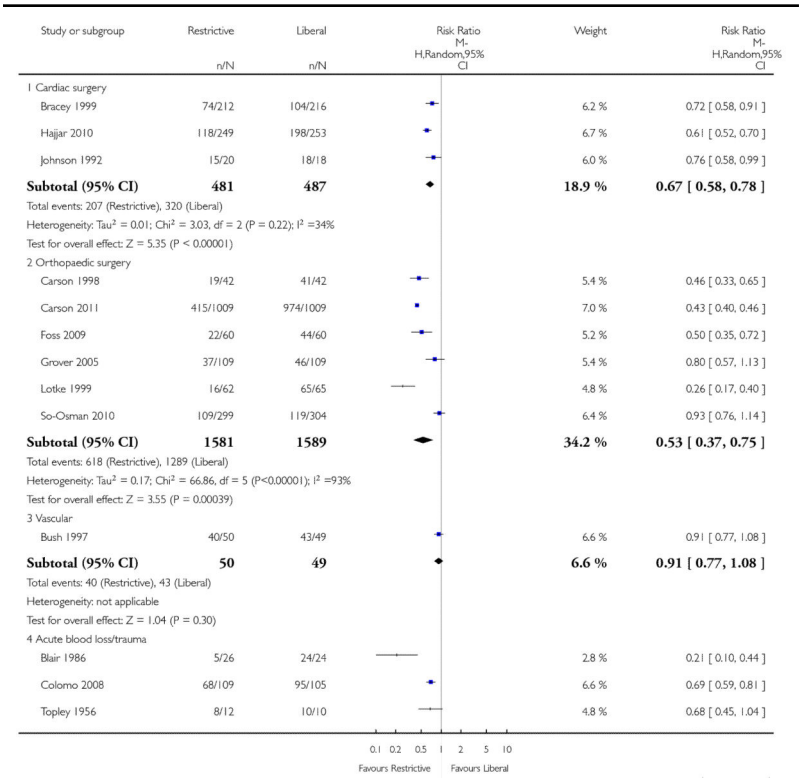
Analysis 1.4

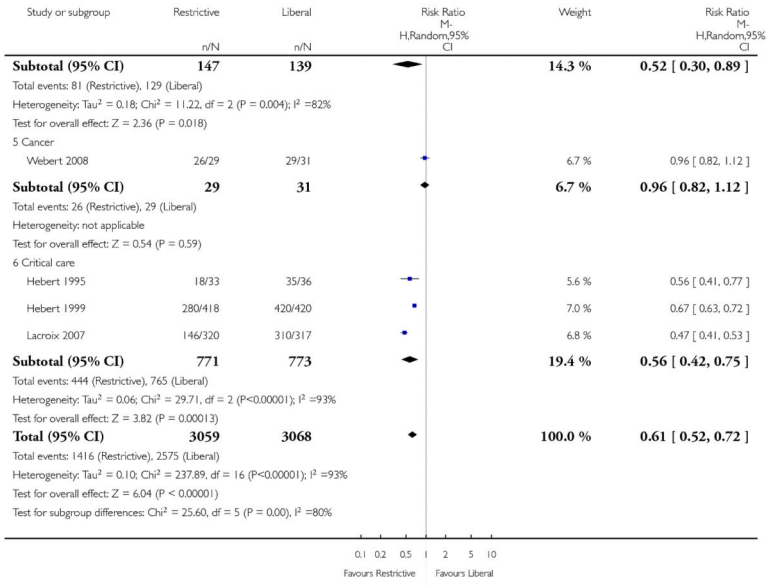
Comparison 1 Blood transfusions, Outcome 4 Patients exposed to blood transfusion (by clinical setting)

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

Comparison: 1 Blood transfusions

Outcome: 4 Patients exposed to blood transfusion (by clinical setting)





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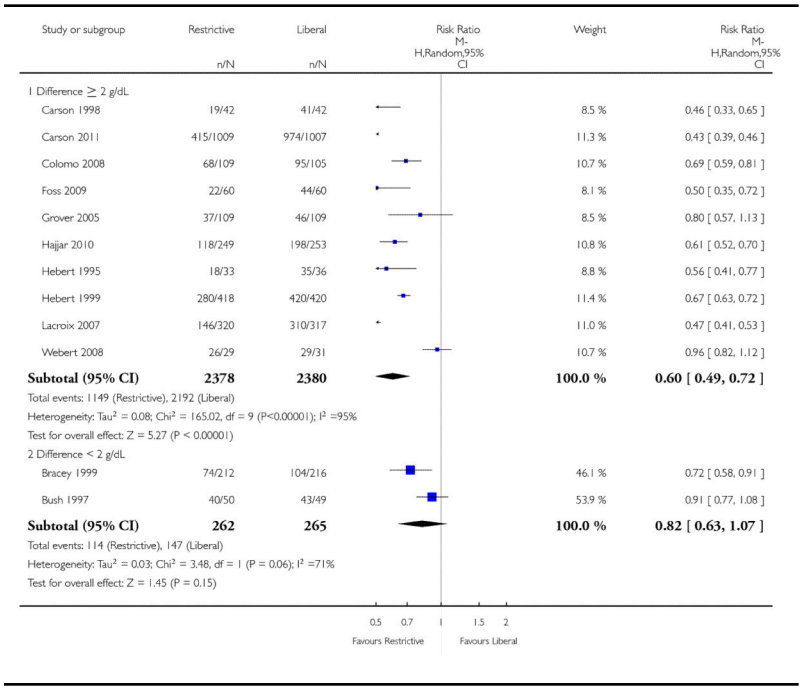
Analysis 1.5

Comparison 1 Blood transfusions, Outcome 5 Patients exposed to blood transfusion (by transfusion threshold)

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

Comparison: 1 Blood transfusions

Outcome: 5 Patients exposed to blood transfusion (by transfusion threshold)



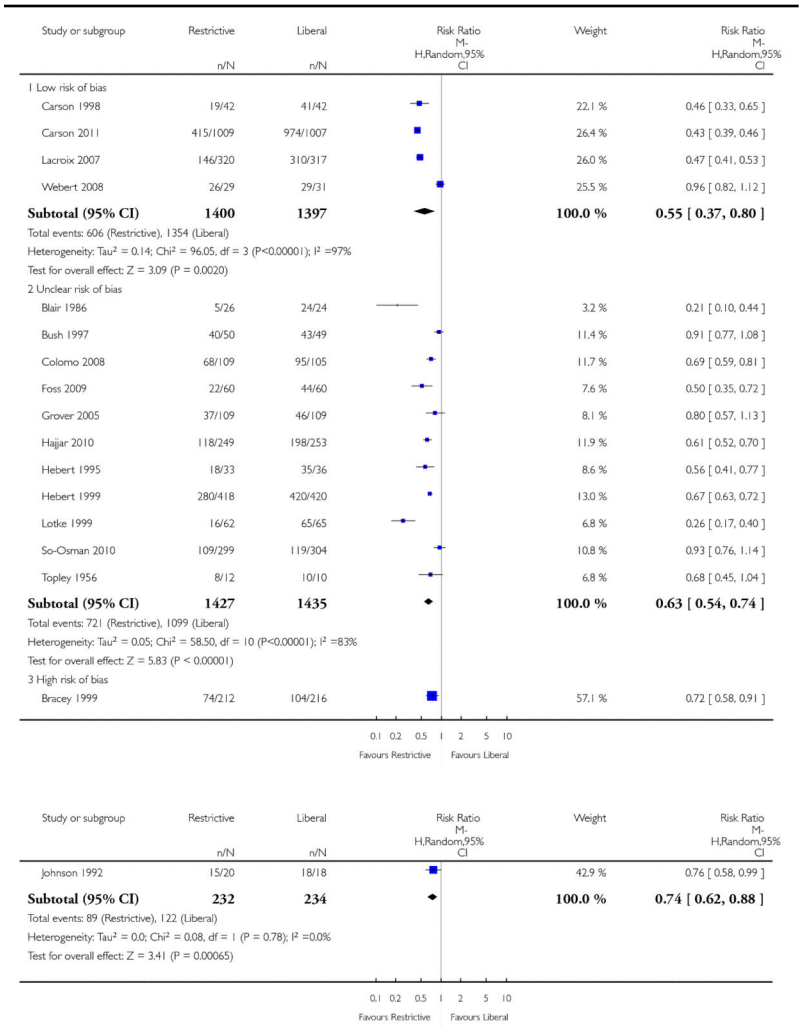
Analysis 1.6

Comparison 1 Blood transfusions, Outcome 6 Patients exposed to blood transfusion (by allocation concealment)

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

Comparison: 1 Blood transfusions

Outcome: 6 Patients exposed to blood transfusion (by allocation concealment)



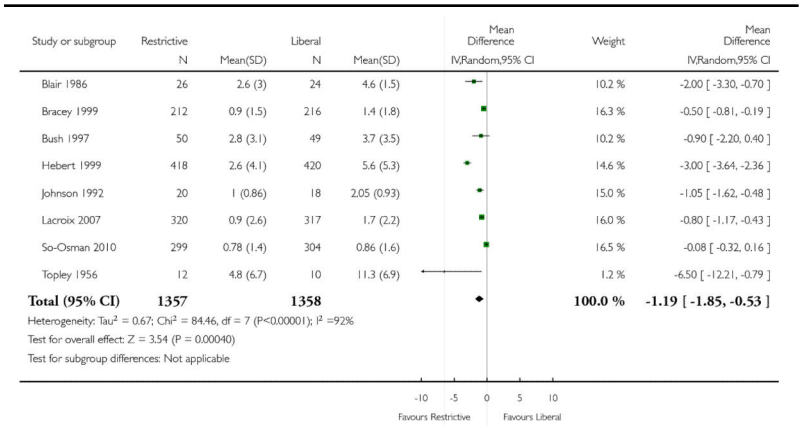
Analysis 1.7

Comparison 1 Blood transfusions, Outcome 7 Units of blood transfused

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

Comparison: 1 Blood transfusions

Outcome: 7 Units of blood transfused



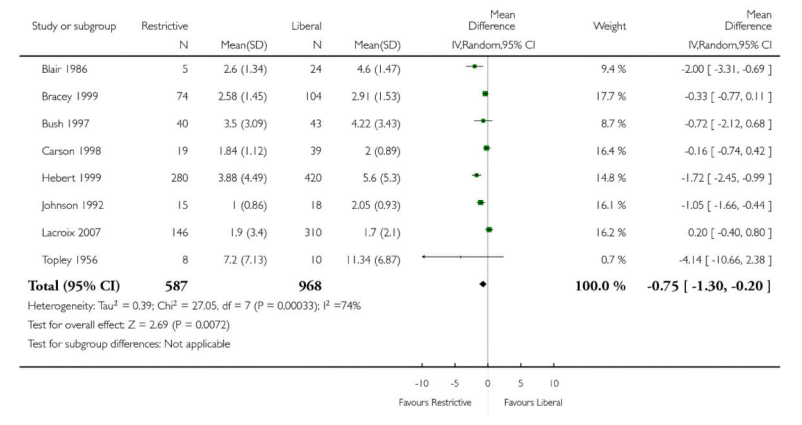
Analysis 1.8

Comparison 1 Blood transfusions, Outcome 8 Units of blood transfused in those transfused

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

Comparison: 1 Blood transfusions

Outcome: 8 Units of blood transfused in those transfused

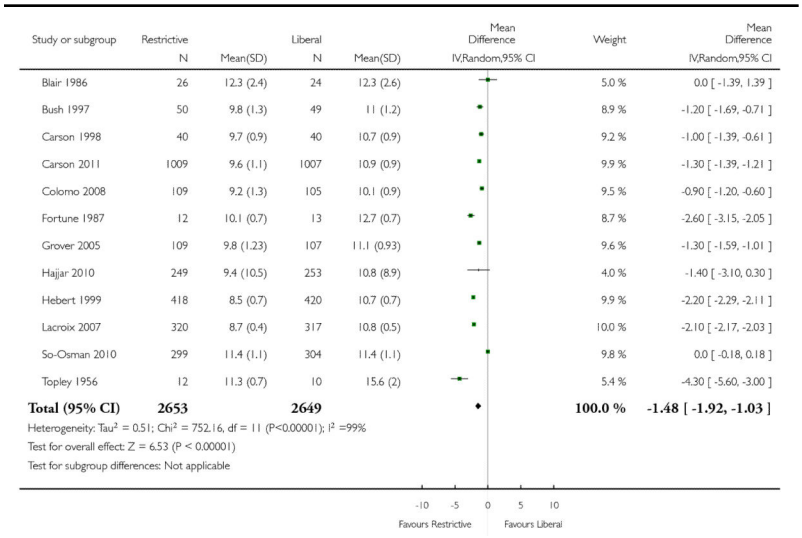


Analysis 2.1
Comparison 2 Haemoglobin concentration, Outcome 1 Haemoglobin concentration

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

Comparison: 2 Haemoglobin concentration

Outcome: 1 Haemoglobin concentration

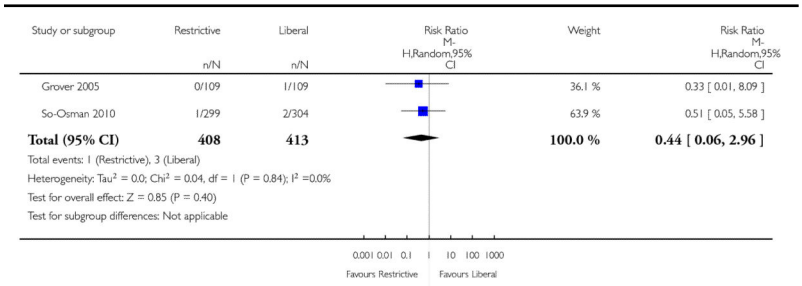


Analysis 3.1
Comparison 3 Mortality, Outcome 1 ≤14-day mortality

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

Comparison: 3 Mortality

Outcome: 1 ≤14-day mortality

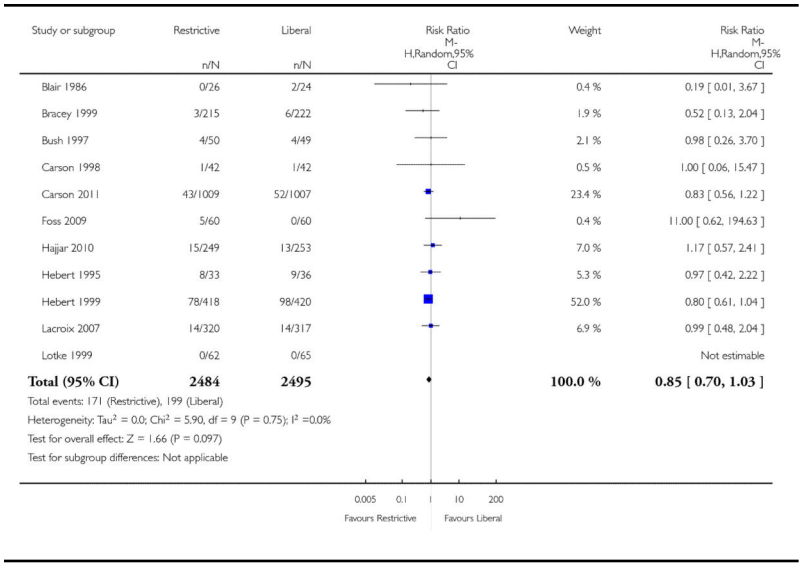


Analysis 3.2
Comparison 3 Mortality, Outcome 2 30-day mortality

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

Comparison: 3 Mortality

Outcome: 2 30-day mortality

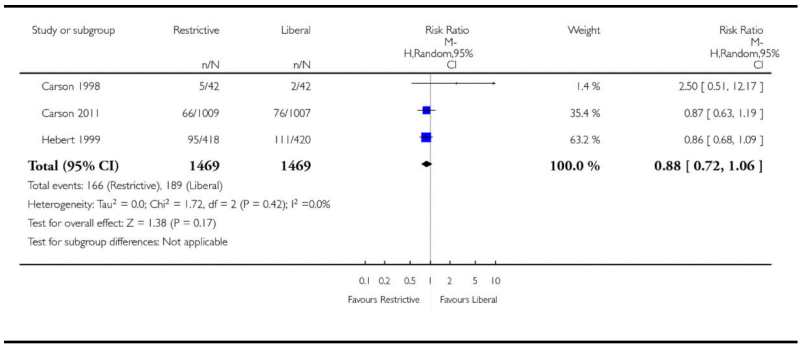


Analysis 3.3
Comparison 3 Mortality, Outcome 3 60-day mortality

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

Comparison: 3 Mortality

Outcome: 3 60-day mortality

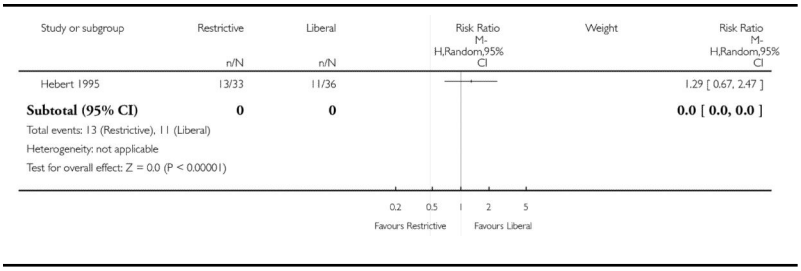


Analysis 3.4
Comparison 3 Mortality, Outcome 4 120-day mortality

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

Comparison: 3 Mortality

Outcome: 4 120-day mortality

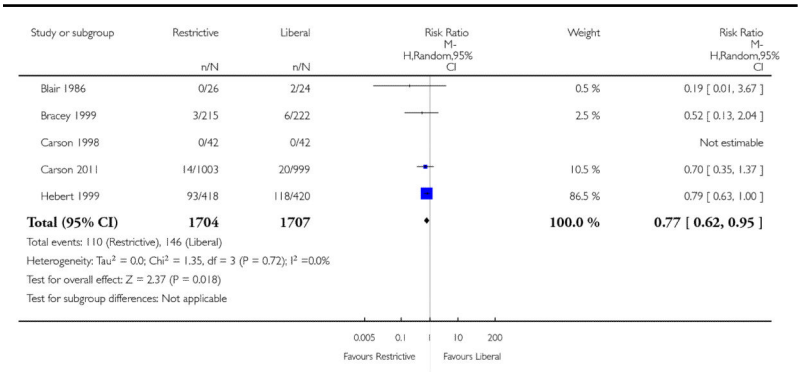


Analysis 3.5
Comparison 3 Mortality, Outcome 5 Hospital mortality

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

Comparison: 3 Mortality

Outcome: 5 Hospital mortality

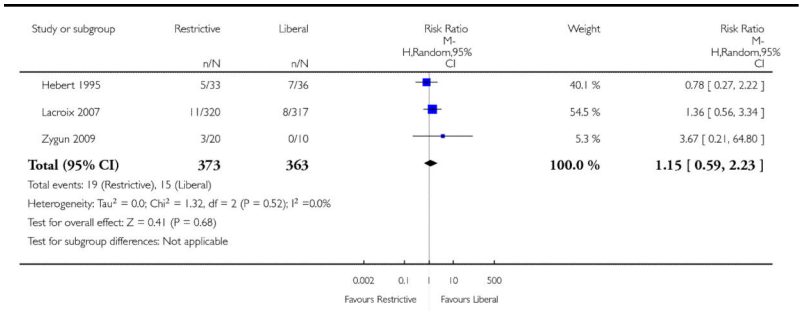


Analysis 3.6
Comparison 3 Mortality, Outcome 6 ICU mortality

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

Comparison: 3 Mortality

Outcome: 6 ICU mortality

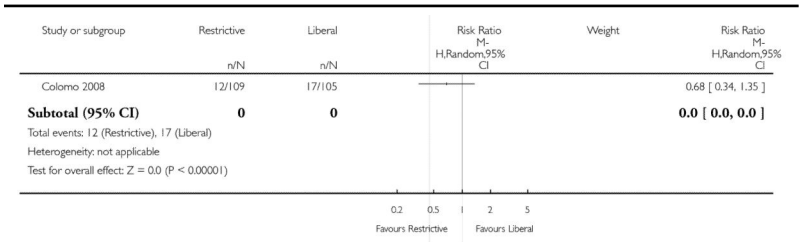


Analysis 3.7
Comparison 3 Mortality, Outcome 7 Mortality (unspecified follow-up period)

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

Comparison: 3 Mortality

Outcome: 7 Mortality (unspecified follow-up period)



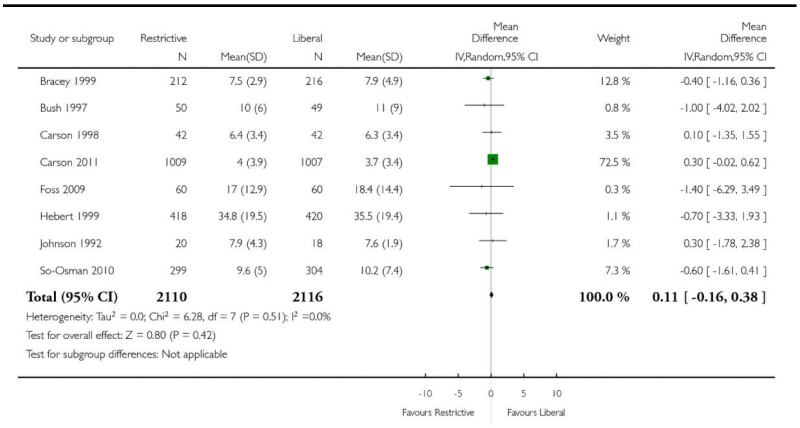
Analysis 4.1

Comparison 4 Length of stay, Outcome 1 Hospital length of stay

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

Comparison: 4 Length of stay

Outcome: 1 Hospital length of stay



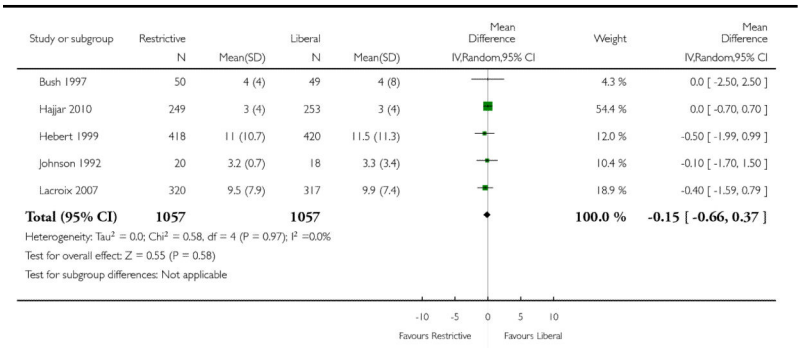
Analysis 4.2

Comparison 4 Length of stay, Outcome 2 ICU length of stay

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

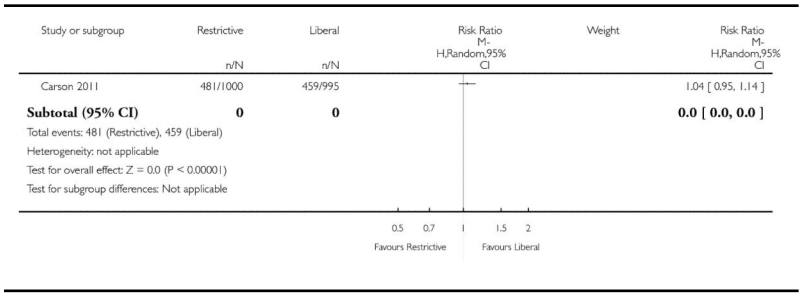
Comparison: 4 Length of stay

Outcome: 2 ICU length of stay



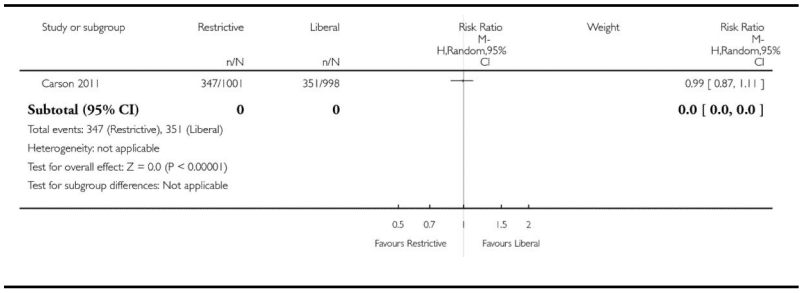
Analysis 5.1
Comparison 5 Function and fatigue, Outcome 1
Inability to walk or death at 30 days

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion
Comparison: 5 Function and fatigue
Outcome: 1 Inability to walk or death at 30 days



Analysis 5.2
Comparison 5 Function and fatigue, Outcome 2
Inability to walk or death at 60 days

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion
Comparison: 5 Function and fatigue
Outcome: 2 Inability to walk or death at 60 days



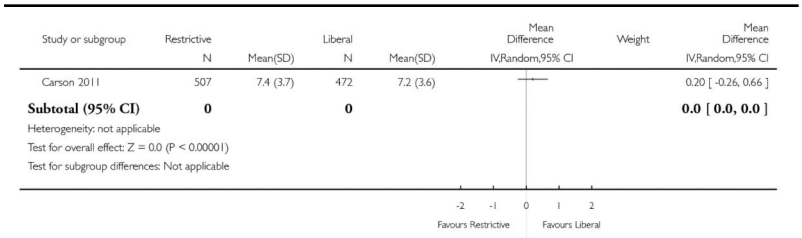
Analysis 5.3

Comparison 5 Function and fatigue, Outcome 3 Lower extremity physical activities of daily living at 30 days

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

Comparison: 5 Function and fatigue

Outcome: 3 Lower extremity physical activities of daily living at 30 days



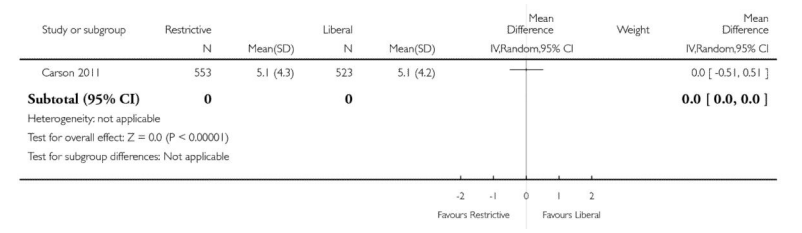
Analysis 5.4

Comparison 5 Function and fatigue, Outcome 4 Lower extremity physical activities of daily living at 60 days

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

Comparison: 5 Function and fatigue

Outcome: 4 Lower extremity physical activities of daily living at 60 days

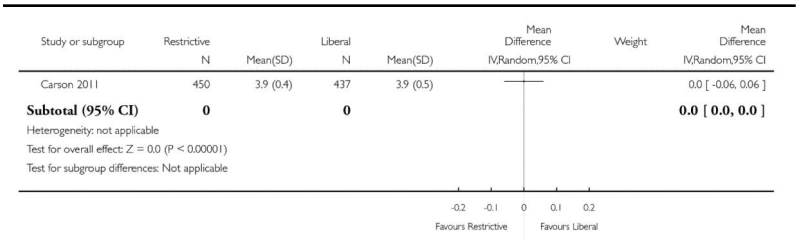


Analysis 5.5
Comparison 5 Function and fatigue, Outcome 5
Instrumental activities of daily living at 30 days

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

Comparison: 5 Function and fatigue

Outcome: 5 Instrumental activities of daily living at 30 days

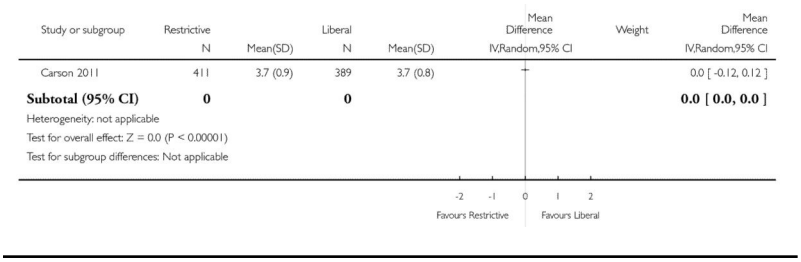


Analysis 5.6
Comparison 5 Function and fatigue, Outcome 6
Instrumental activities of daily living at 60 days

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

Comparison: 5 Function and fatigue

Outcome: 6 Instrumental activities of daily living at 60 days



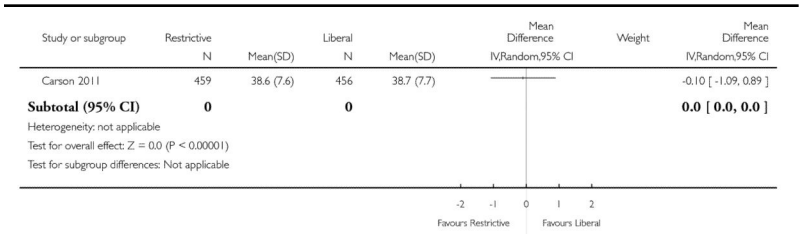
Analysis 5.7

Comparison 5 Function and fatigue, Outcome 7 Energy/fatigue at 30 days

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

Comparison: 5 Function and fatigue

Outcome: 7 Energy/fatigue at 30 days



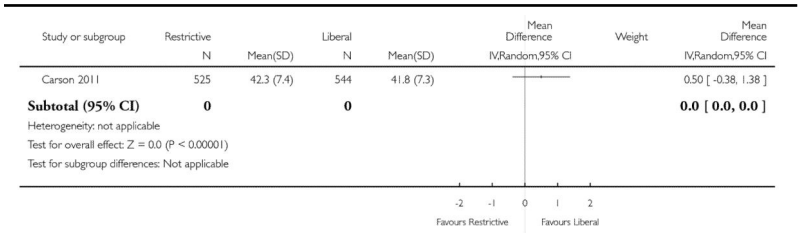
Analysis 5.8

Comparison 5 Function and fatigue, Outcome 8 Energy/fatigue at 60 days

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

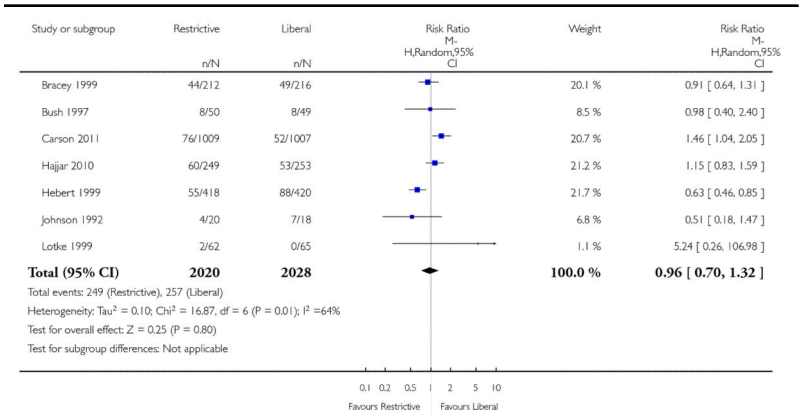
Comparison: 5 Function and fatigue

Outcome: 8 Energy/fatigue at 60 days



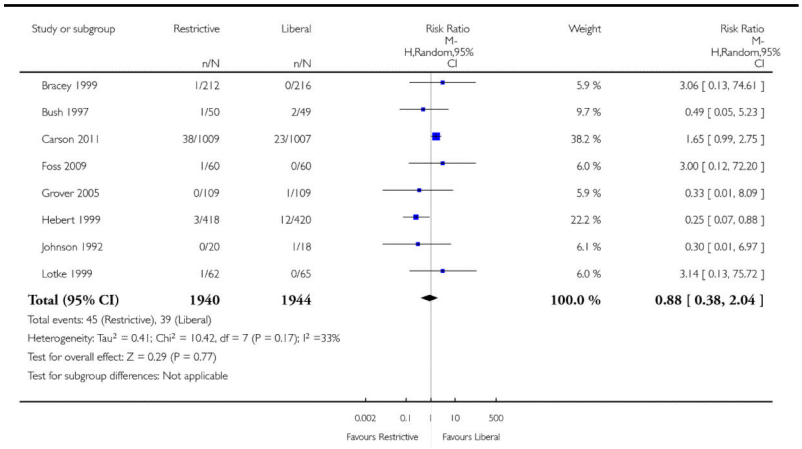
Analysis 6.1
Comparison 6 Adverse events, Outcome 1 Cardiac events

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion
Comparison: 6 Adverse events
Outcome: 1 Cardiac events



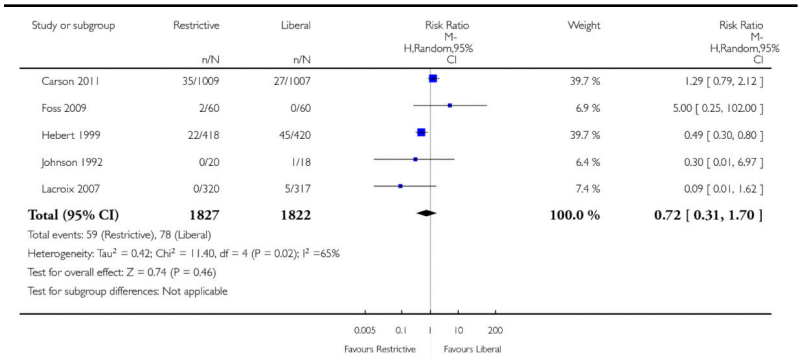
Analysis 6.2
Comparison 6 Adverse events, Outcome 2 Myocardial infarction

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion
Comparison: 6 Adverse events
Outcome: 2 Myocardial infarction



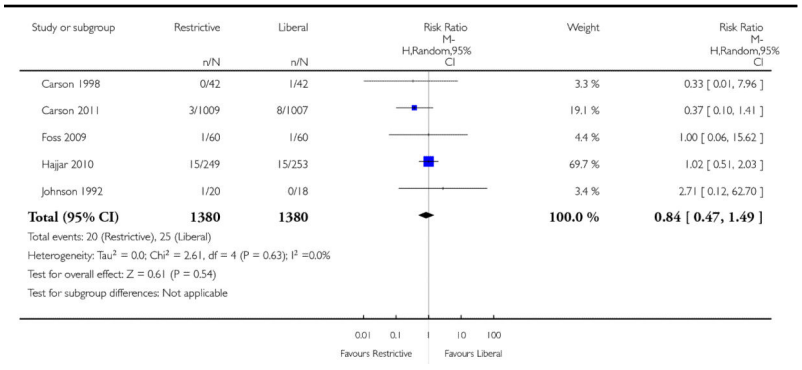
Analysis 6.3
Comparison 6 Adverse events, Outcome 3 Pulmonary oedema

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion
Comparison: 6 Adverse events
Outcome: 3 Pulmonary oedema



Analysis 6.4
Comparison 6 Adverse events, Outcome 4 Cerebrovascular accident (CVA) - stroke

Review: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion
Comparison: 6 Adverse events
Outcome: 4 Cerebrovascular accident (CVA) - stroke

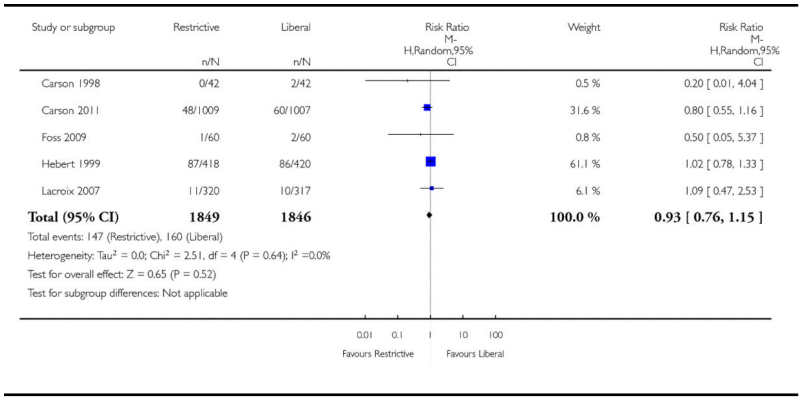


Analysis 6.5
Comparison 6 Adverse events, Outcome 5 Pneumonia

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

Comparison: 6 Adverse events

Outcome: 5 Pneumonia

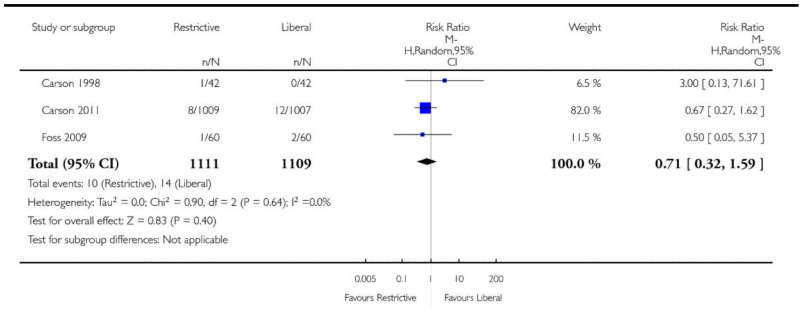


Analysis 6.6
Comparison 6 Adverse events, Outcome 6 Thromboembolism

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

Comparison: 6 Adverse events

Outcome: 6 Thromboembolism

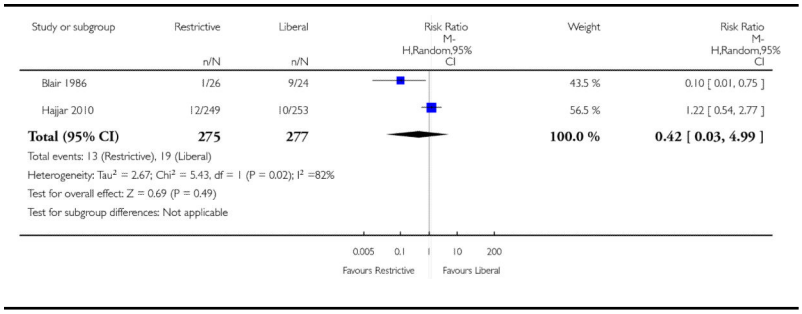


Analysis 6.7
Comparison 6 Adverse events, Outcome 7 Rebleeding

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

Comparison: 6 Adverse events

Outcome: 7 Rebleeding

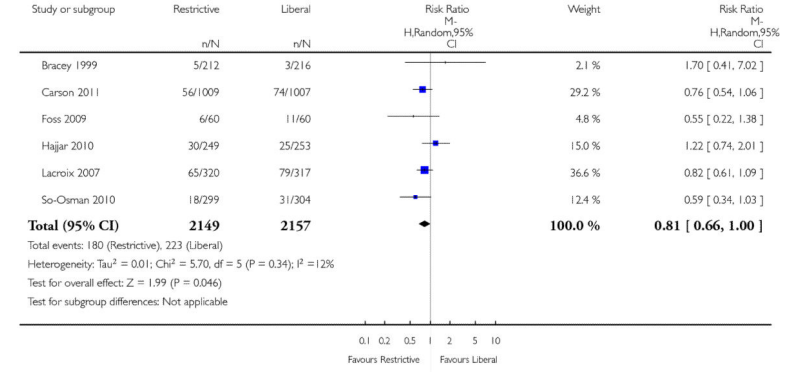


Analysis 6.8
Comparison 6 Adverse events, Outcome 8 Infection

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

Comparison: 6 Adverse events

Outcome: 8 Infection

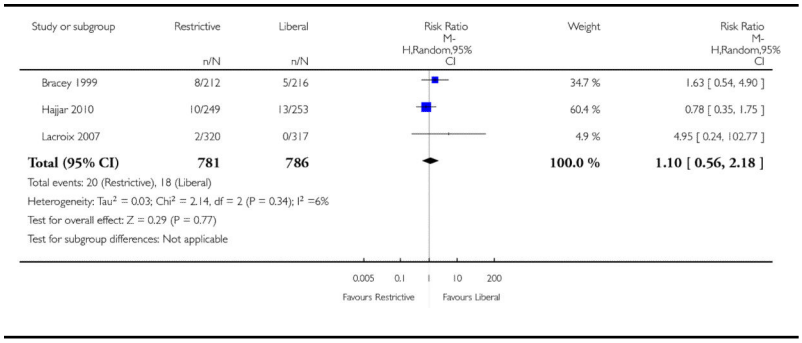


Analysis 6.9
Comparison 6 Adverse events, Outcome 9 Renal failure

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

Comparison: 6 Adverse events

Outcome: 9 Renal failure

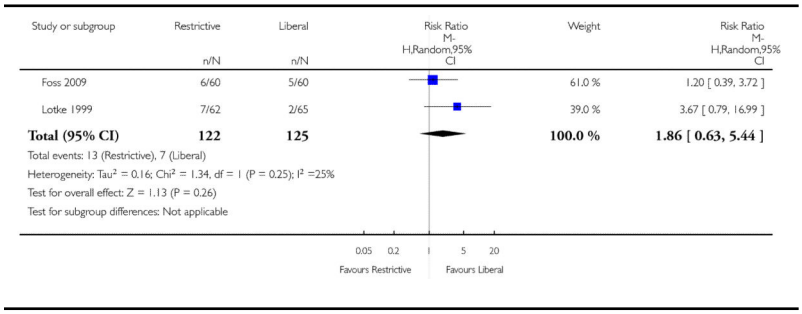


Analysis 6.10
Comparison 6 Adverse events, Outcome 10 Mental confusion

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

Comparison: 6 Adverse events

Outcome: 10 Mental confusion



WHAT'S NEW

Last assessed as up-to-date: 1 February 2011.

Date	Event	Description
17 April 2012	Amended	Minor copy edits were made to the text.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 2, 2002

Date	Event	Description
20 December 2011	New citation required and conclusions have changed	The searches were updated to February 2011. Data from two new trials are included and the results have been amended accordingly. One trial was identified through the updated search; the other had previously been included as an ongoing trial and the results recently became available The Background section of the review has been updated. The overall conclusions of the review remain similar but the clinical settings for which the results can be generalised have been extended As part of this update the assessment of methodological quality used in earlier versions of this review has been replaced with an assessment of the risk of bias. This amendment is in accordance with a change in the Cochrane Collaboration's methodological guidance The authors of the review have changed.
1 February 2011	New search has been performed	The search for studies was updated to February 2011.
9 September 2008	Amended	Converted to new review format.
17 November 2004	New search has been performed	An updated search for new trials was conducted in November 2004. No new trials for inclusion were identified

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences identified.

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Restricting the use of blood transfusion

Many people are given a transfusion of blood from an unrelated donor as part of their medical treatment. There are, however, risks involved. In particular, infections (including HIV and certain types of hepatitis) may be passed on to the person receiving the blood. This risk is very small in high-income countries but much larger in poor countries which do not test the blood for infections. Because of the risks, doctors try to avoid giving blood unless it is really necessary. One approach is to give the transfusion only if the amount of haemoglobin in the patient's blood has dropped below a certain 'threshold' level. We looked for controlled studies comparing the effectiveness of giving more versus less blood. We found 19 studies, with a total of 6264 patients. We conclude that, for most patients, giving less blood is safe and blood transfusion is probably not essential until haemoglobin levels drop below 7.0 to 8.0 grams per decilitre. As no trials have been done involving patients with an acute heart problem, it is not currently known how much blood to give these patients.

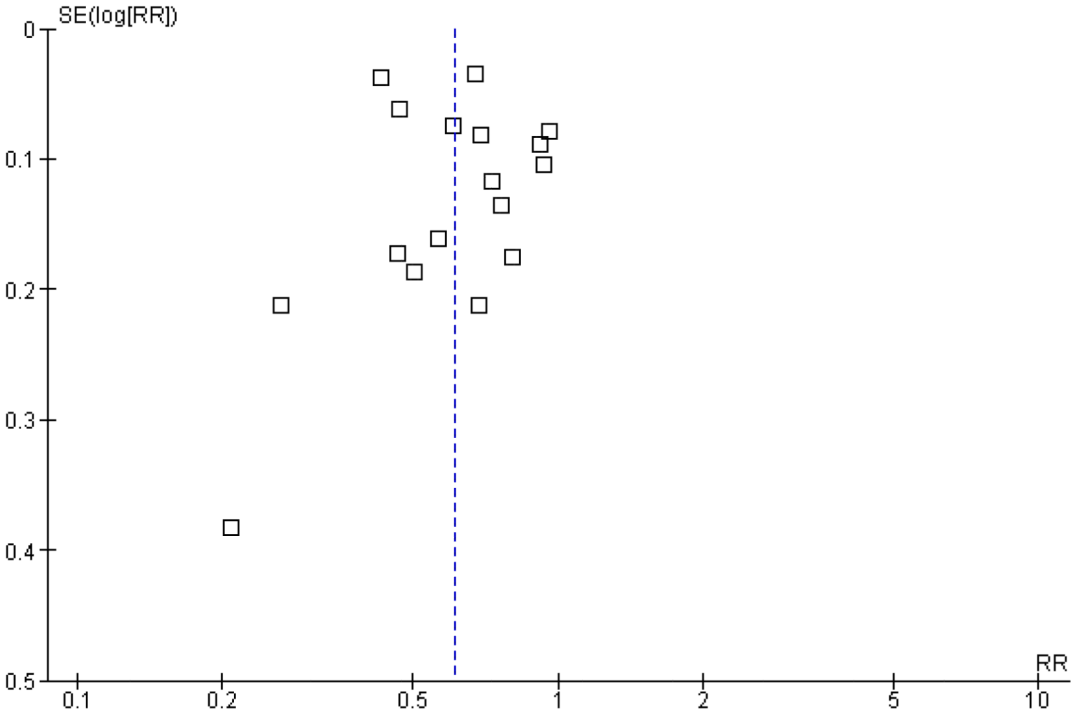

Figure 1. Funnel plot of comparison 1.1 Patients exposed to blood transfusion (all studies)

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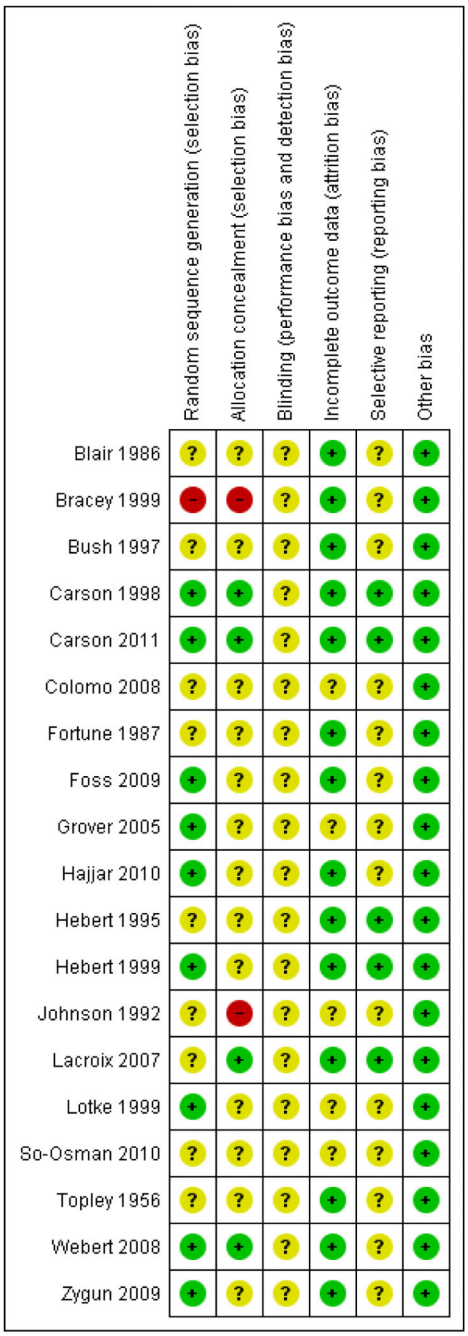

Figure 2. 'Risk of bias' summary: review authors' judgements about each methodological quality item for each included study

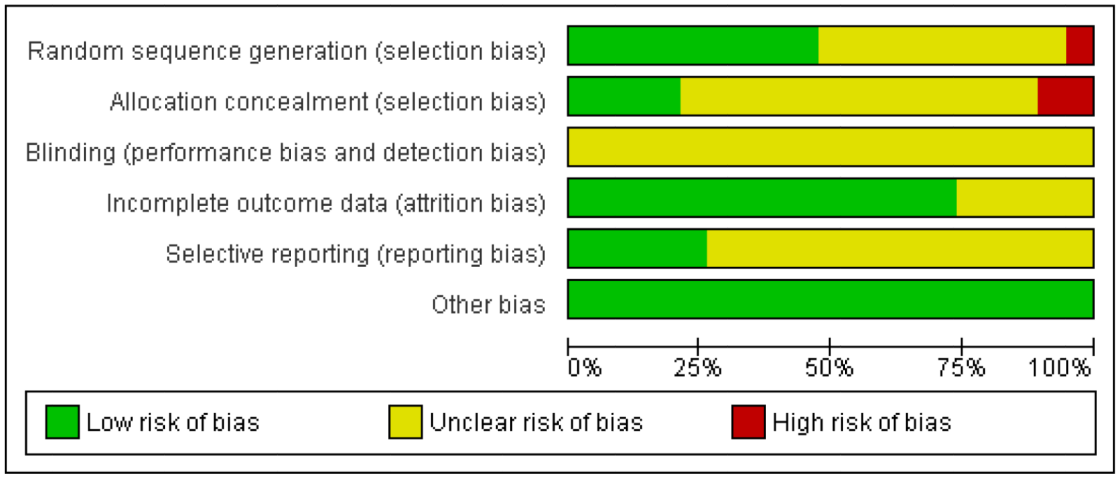

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Nineteen studies are included in this review

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