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**Indications for Red Cell Transfusion in Cardiac Surgery: A Systematic Review and Meta-Analysis of Randomised Controlled Trials and Observational Studies.**

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## **Abstract**

**Background:** Good blood management is an important determinant of outcome in cardiac surgery. Current guidelines recommend restrictive red blood cell (RBC) transfusion practice. Our objective was to systematically review the evidence from randomised controlled trials (RCTs) and observational studies that are used to inform transfusion decisions in adult cardiac surgery.

**Methods:** We searched electronic databases (PUBMED, EMBASE, Cochrane Library, DARE) from inception to May 2015, databases from specialist societies, and bibliographies of included studies and recent relevant review articles. RCTs that evaluated the effect of liberal versus restrictive RBC transfusion threshold in cardiac and non-cardiac surgery patients, and observational studies that evaluated the effect of RBC transfusion compared with no transfusion on postoperative outcomes in adult cardiac surgery patients were included. Adjusted odds ratios were pooled using fixed- and random-effects meta-analyses.

**Findings:** Data from 6 cardiac surgical RCTs (3352 patients), 19 non-cardiac surgical RCTs (8361 patients), and 39 observational studies (232 806 patients) were included. The pooled mortality odds ratios comparing liberal versus restrictive transfusion thresholds were 0.70 (95% CI 0.49–1.02,  $p=0.06$ ) and 1.10 (95% CI 0.96–1.27,  $p=0.16$ ) for cardiac surgical RCTs and RCTs in settings other than cardiac surgery, respectively. By contrast, observational cohort studies in cardiac surgery found that RBC transfusion compared with no transfusion was associated with substantially higher mortality (OR 2.72; 95% CI 2.11–3.49,  $p<0.001$ ) and other morbidity, although with substantial heterogeneity and small study effects.

**Interpretation:** Evidence from RCTs in cardiac surgery refutes findings from observational studies that RBC transfusion is associated with a substantially increased risk of mortality and morbidity. Such studies, and RCTs in non-cardiac surgery, should not be used to inform treatment decisions or guidelines for cardiac surgery patients.

**Funding:** There was no funding source for this study.

## **Introduction**

The aim of perioperative red blood cell (RBC) transfusion in cardiac surgery is to improve or preserve oxygen delivery in the setting of blood loss and anaemia. The decision to transfuse is complicated by several factors; severe anaemia and excessive blood loss are common in this setting<sup>1,2</sup>, and patients with cardiovascular disease have different transfusion requirements to other patient groups<sup>3</sup>. Transfusion decisions in cardiac surgery are most commonly based on the severity of perioperative anaemia: guidelines currently recommend (Grade C recommendation) highly restrictive transfusion thresholds with Haemoglobin (Hb) concentrations of 6-7g/dL<sup>4,5</sup>. These are based largely on the results of RCTs in non-cardiac surgery patients that indicate equivalence for restrictive transfusion thresholds<sup>6-8</sup>. They are also influenced by evidence from observational studies showing strong associations between the reversal of severe anaemia by RBC transfusion with adverse clinical outcomes, such as death, acute lung injury, acute kidney injury, stroke, myocardial infarction, sepsis, and surgical site infections<sup>9-11</sup>.

RBC transfusion has important morbidity; haemolytic transfusion reactions and Transfusion Associated Lung Injury account for a significant number of deaths per year<sup>12</sup> but a causal relationship between RBC transfusion and the adverse outcomes suggested by observational analyses has yet to be established. Severe anaemia, the main indication for transfusion, is also an important predictor of adverse outcomes in cardiac surgery, where patients who have symptomatic cardiac disease are already at the limits of their physiological reserve<sup>2,11</sup>. Clinical uncertainty as to the appropriate indications

for transfusion is reflected in wide variations in transfusion rates in cardiac surgery; ranging from 25% to 95% between hospitals in contemporary cross sectional studies <sup>13</sup>.

The aims of this study were to systematically review and critically evaluate the evidence from RCTs and observational studies that are used to inform transfusion guidelines in cardiac surgery, and hence to provide evidence to support clinical transfusion decisions as well as to inform the design of future studies of appropriate transfusion indicators.

## **Methods**

A protocol was developed (eAppendix pg 21) that was restricted to RCTs and observational studies of transfusion in cardiac surgery, but because current transfusion guidelines <sup>4,5</sup> are also based on RCTs in non-cardiac surgical patients, we subsequently decided to include these in this systematic review. Despite the limitations of comparing different study designs, we chose to compare RCTs and observational studies as these are the evidence base for current guidelines. The study adhered to MOOSE (eAppendix pg 29) and PRISMA (eAppendix pg 31) guidelines <sup>14,15</sup>. Two investigators (VSA, NNP) independently assessed studies for eligibility, risk of bias and data extraction: disagreements were resolved by discussion.

### *Study Identification*

We attempted to identify all relevant published RCTs and controlled observational (non-randomised) cohort and case-control studies evaluating the impact of RBC transfusion on post-operative outcomes in adult cardiac surgical patients and non-cardiac surgical patients (RCTs only). We searched electronic databases (PUBMED, EMBASE, Cochrane

Library, DARE) from inception to May 2015. Search terms are described in the eAppendix pg 23. To identify RCTs in non-cardiac surgical patients, we re-ran the searches excluding terms relevant to the procedure (e.g. cardiac surgery) and limited the search to RCTs. We also searched relevant transfusion electronic databases. We checked the bibliographies of included studies and recent review articles for additional relevant articles.

### *Study Selection*

Inclusion criteria were (1) Adult patients undergoing cardiac surgery (RCTs and observational studies) or critically ill/non-cardiac surgical patients (RCTs only), (2) Allogeneic RBC transfusion (intra- or post-operative), (3) In RCTs the comparison was liberal versus restrictive transfusion threshold and in observational studies the comparison was RBC transfusion versus no RBC transfusion. Exclusion criteria are provided in eAppendix pg 21. Studies evaluating the effects of storage duration on outcome were excluded as these compared outcomes in patients receiving “old blood” and “young blood”: they did not include data for patients who received “no transfusion”.

### *Assessment of Risk of Bias*

RCTs were assessed using the Cochrane Collaboration’s Risk of Bias tool<sup>16</sup>.

Observational studies were assessed using the Newcastle-Ottawa Scales (NOS) for cohort and case-control studies.

### *Data Extraction*

Data extraction was done independently by 2 reviewers and included author, year of publication, country of origin, study design, sample size, inclusion and exclusion criteria, methods of statistical adjustment, transfusion rate, and study results. We also noted variables included for statistical adjustment in observational studies, particularly anaemia and bleeding. Data on the transfusion of non-red cell components was not extracted as it was not our primary objective to explore the interaction between red cell and non-red cell transfusions, but to focus on the effects of red cell transfusion on clinically important endpoints such as death, major morbidity and resource use.

### *Outcomes*

The primary outcome was short-term mortality. The secondary outcomes were acute myocardial infarction (MI), pulmonary morbidity (including adult respiratory distress syndrome, acute lung injury, delayed extubation), acute kidney injury (AKI) (including all stages of AKI, AKI requiring renal replacement therapy), infectious morbidity (including deep sternal wound infection, leg wound infection, sepsis), and cerebrovascular accident (CVA).

### *Statistical Analysis*

Pooled odds ratios (OR) and 95% confidence intervals were estimated using both fixed- and random-effects meta-analyses. Where possible, we aimed to pool adjusted odds ratios from observational studies; otherwise we used raw outcome data to estimate unadjusted odds ratios. Sensitivity analyses explored the robustness of results by comparing the results of fixed- and random-effects meta-analyses. We tested for and quantified heterogeneity using the Q and  $I^2$  statistics respectively<sup>17</sup>. Small study effects



were assessed by visual inspection of funnel plots and using the Egger test. The Trim and fill method was not used, although it was pre-specified in the protocol, as it is known to perform poorly in the presence of substantial between-study heterogeneity and we therefore concluded that it would not be appropriate to use it for these data.

Analyses were stratified by study design (cardiac surgical RCT, non-cardiac surgical RCT, cohort studies, and case control studies) and cardiac disease state (RCTs exclusively recruiting patients with active cardiac disease versus those RCTs not recruiting patients with active cardiac disease). Differences between groups of studies were quantified using random-effects meta-regression. Potential explanatory variables considered included: study design, transfusion thresholds and number of RBC units transfused. In addition, we used the approach of Greenland and Longnecker<sup>18</sup> to estimate a dose-response effect in each study that provided useable data, and then pooled these estimates across studies. Subgroup analyses were performed by sample size, country, statistical adjustments, year of enrolment of first patient, and number of transfused RBC units. All analyses were carried out using MIX Version 2.0<sup>19</sup> and Stata 10.0 (Statacorp, College Station, Texas).

#### *Role of Funding Source*

There was no funding source for this study. All authors had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

## **Results**

### *Characteristics of studies*

A total of six cardiac surgical RCTs<sup>20-25</sup> (3352 patients), 19 non-cardiac surgical RCTs (8361 patients)<sup>3,6-8,26-38</sup> and 39 cardiac surgical observational studies<sup>9-11,39-74</sup> (232 806 patients) met the inclusion criteria. A flow diagram depicting the overall search strategy is provided in Figure 1 and characteristics of included studies are shown in the eAppendix pg 2. All cardiac surgical RCTs compared restrictive with liberal RBC transfusion strategies. Four RCTs included only low-risk surgical patients undergoing elective cardiac or coronary surgery and thus excluded patients at highest risk of requiring RBC transfusion. Only two RCTs included high risk patients defined by a CARE score greater than 3<sup>20</sup> or including all patients except those undergoing emergency procedures<sup>25</sup>. One RCT used non-leucodepleted RBCs<sup>21</sup> and another RCT used leucodepleted RBCs<sup>25</sup>. All cardiac surgical RCTs were classified as recruiting patients with active cardiac disease. There was no significant difference in postoperative bleeding between groups (eAppendix pg 7). The median number of RBC units transfused per patient ranged from 1 to 3.

All non-cardiac surgical RCTs compared restrictive with liberal RBC transfusion strategies. Five RCTs evaluated outcomes in orthopaedic patients, five in critical care patients, three in paediatric patients, two in patients with myocardial infarction, two in patients with upper gastrointestinal haemorrhage, and one each in patients admitted because of trauma or needing vascular surgery. Nine RCTs transfused leucodepleted RBCs. Two RCTs exclusively recruited patients with active cardiac disease (myocardial infarction).

Among the observational studies, 21 cohort and 18 case control studies met the inclusion criteria. Thirty-five were retrospective studies that extracted baseline and outcome data from databases of routinely collected patient information. In general, observational studies included all patients undergoing cardiac surgery, including those requiring urgent or emergent surgery, impaired LV function, preoperative anaemia or organ dysfunction, redo surgery, and massive blood loss. All observational studies compared patients who did and did not receive RBC transfusion. Only one study stated that all RBCs administered to participants were leucodepleted<sup>45</sup>. Only 12 studies reported numbers of RBC units transfused: the median number per patient ranged from 3 to 8.

### *Risk of Bias*

The risk of bias assessment of all RCTs is shown in the eAppendix pg 8. Eighteen of 25 studies reported adequate methods of random sequence generation and 15 studies reported adequate methods of allocation concealment. Most studies did not clearly report blinding of participants and blinding of outcome assessment. The reporting and handling of missing data was detailed for 22 studies. Three cardiac surgical studies explicitly reported adherence to a transfusion protocol. The 2 largest cardiac surgical RCTs were judged to be low risk for all elements of the risk of bias tool apart from reporting of adherence which was poorly described in one trial<sup>21,25</sup>.

The quality assessment of all observational studies is shown in the eAppendix pg 9. With regard to cohort studies, 14 of 21 studies (67%) were assessed to be of high quality (NOS score higher than 6). All observational studies adjusted for common risk factors

associated with mortality following cardiac surgery. However, over 90% of cohort studies either completely or partly failed to adjust for important confounders related to transfusion and mortality. These include the severity of preoperative (n=11/21 studies) and intraoperative (n=13/21) anaemia, and bleeding (n=16/21). In case-controlled studies, 14 of 18 studies (78%) were assessed to be of high quality. However, all studies failed to adjust for at least one of the following potential confounders in their analyses: the severity of preoperative (n=14/18 studies) and intraoperative (n=16/18) anaemia, or bleeding (n=12/18)(eTable 3). None of the observational studies attempted to adjust for potential lead-time bias.

#### *RBC Transfusion and adverse outcomes in RCTs and observational studies*

Based on the results of five cardiac surgical RCTs, the pooled mortality odds ratio for the comparison liberal versus restrictive transfusion thresholds was 0.70 (95% CI 0.49-1.02, p=0.06). There was no evidence of between-study heterogeneity ( $I^2=0\%$ ) (Figure 2, Table 1).

By contrast, based on the results of 19 RCTs in non-cardiac surgical patients the pooled mortality odds ratio for the comparison liberal versus restrictive transfusion thresholds was 1.10 (95% CI 0.96-1.27, p=0.16). There was some evidence of between study heterogeneity ( $I^2=30\%$ )(Figure 2, Table 1). After combining all trials (cardiac and non-cardiac surgical RCTs) there was no evidence that the risk of mortality differed between patients randomised to liberal or restrictive transfusion strategies (random effects OR 1.00, 95% CI 0.82-1.21) (Figure 2).

To test the hypothesis that liberal transfusion thresholds may benefit patients with active cardiac disease, we performed a post-hoc subgroup analysis of RCTs stratified by active cardiac disease state. Based on a meta-analysis of seven RCTs in patients with active cardiac disease (five cardiac surgical trials and two trials recruiting myocardial infarction patients), there was evidence that liberal RBC transfusion led to a reduction in mortality compared with restrictive transfusion strategies (OR 0.67, 95% CI 0.47-0.95,  $p=0.03$ ). There was little evidence of between study heterogeneity ( $I^2=2\%$ ) (eAppendix pg 11). By contrast, meta-analysis of 12 RCTs recruiting patients with stable cardiac disease or no cardiac disease provided evidence that liberal RBC transfusion significantly increased mortality compared with restrictive transfusion strategies (OR 1.17, 95% CI 1.01-1.36,  $p=0.04$ ). There was moderate between study heterogeneity ( $I^2=28\%$ ). A meta-regression found a significant reduction in mortality associated with liberal transfusion in RCTs recruiting patients with compared to without active cardiac disease (ratio of ORs: 0.57, 95% CI 0.36 – 0.91,  $p=0.02$ ).

Based on a random-effects meta-analysis of results from 16 observational cohort studies in cardiac surgery patients, RBC transfusion was associated on average with a substantial increase in mortality compared with no transfusion (random effects OR 2.72, 95% CI 2.11 - 3.49,  $p<0.001$ , Figure 3 and Table 1). There was substantial heterogeneity between results of cohort studies ( $I^2=93\%$ ), and smaller observational studies tended to estimate the adverse effect of RBC transfusion to be greater than did larger studies (Egger test P value 0.02, eAppendix pg 12), for which reason the fixed-effect estimate of the association between RBC transfusion and mortality was substantially attenuated (OR 1.63, 95% CI 1.56 – 1.70,  $p<0.001$ ), compared with the random-effects estimate<sup>75</sup>.

There was substantial heterogeneity ( $I^2=98\%$ ) between the associations estimated in three case-control studies. The association of RBC transfusion with mortality was significantly higher in cohort studies than was the effect of liberal compared with restrictive transfusion estimated in cardiac surgical RCTs (ratio of ORs: 3.11, 95% CI 1.87 – 5.19,  $p<0.001$ ).

Among the six cardiac surgical RCTs there was no evidence that liberal RBC transfusion led to increased pulmonary morbidity compared to restrictive transfusion strategies (OR 0.94, 95% CI 0.76–1.17,  $p=0.58$ ). There was no evidence of between-study heterogeneity ( $I^2=0\%$ ) (Table 1 and eAppendix pg 13). Similarly, seven RCTs in non-cardiac surgical patients suggested that liberal RBC transfusion did not increase pulmonary morbidity compared to restrictive transfusion strategies (OR 1.15, 95% CI 0.95–1.40,  $p=0.14$ ,  $I^2=18\%$ ). By contrast, random-effects meta-analysis of results from seven observational studies suggested that on average RBC transfusion was associated with a substantial increase in pulmonary morbidity (average OR 1.99, 95% CI 1.47–2.69,  $p<0.001$ , Table 1 and eAppendix pg 13) with evidence of significant heterogeneity between results ( $I^2=97\%$ ).

There was no evidence from cardiac surgical RCTs that liberal transfusion led to increased AKI (5 RCTs: OR 0.86, 95% CI 0.68–1.09,  $p=0.22$ ) or infectious morbidity (4 RCTs: OR 0.97, 95% CI 0.79–1.19,  $p=0.75$ ) compared to restrictive transfusion strategies, and no evidence of between-study heterogeneity (Table 1, eAppendix pg 14 and 15). Amongst 11 RCTs in non-cardiac surgical patients the pooled infectious morbidity odds ratio for the comparison liberal versus restrictive transfusion was 1.16

(95% CI 0.99-1.37,  $p=0.07$ ,  $I^2=0\%$ ). By contrast, random-effects meta-analysis of results from observational studies suggested that on average RBC transfusion was associated with a substantial increase in AKI (14 observational studies: OR 3.05, 95% CI 2.10-4.44,  $p<0.001$ ) and infectious morbidity (11 observational studies: OR 2.30, 95% CI 1.85 – 2.86,  $p<0.001$ ). There was substantial heterogeneity between results of observational studies (AKI:  $I^2=97\%$ ; Infection:  $I^2=73\%$ ) and smaller observational studies tended to estimate the adverse effect of RBC transfusion to be greater than did larger observational studies (AKI: Egger test P value 0.075; Infection: Egger test P value 0.037, eAppendix pg 16 and 17.). Correspondingly, the fixed-effect estimates of the associations between RBC transfusion and AKI (OR 1.73, 95% CI 1.65-1.83,  $p<0.001$ ), and RBC transfusion and infection (OR 1.81, 95% CI 1.73-1.89,  $p<0.001$ ) were substantially attenuated, compared with the random-effects estimates.

Only 1 cardiac surgical RCT reported on MI and CVA. There was no evidence from non-cardiac surgical RCTs that liberal transfusion led to increased MI (10 RCTs: OR 0.79, 95% CI 0.58-1.09,  $p=0.15$ ) or CVA (8 RCTs: OR 1.53, 95% CI 0.83–2.83,  $p=0.18$ ) compared to restrictive transfusion strategies, and no evidence of between-study heterogeneity (Table 1, eAppendix pg 18 and 19). Random-effects meta-analysis of results from observational studies suggested that on average RBC transfusion was associated with an increase in MI (8 observational studies: OR 1.93, 95% CI 1.45-2.58,  $p<0.001$ ) and CVA (7 observational studies: OR 2.03, 95% CI 1.42-2.90,  $p<0.001$ ) with substantial heterogeneity between study results (MI:  $I^2=89\%$ ; CVA:  $I^2=79\%$ ) (Table 1, eAppendix pg 18 and 19).

### *Sources of Heterogeneity*

Pooled analysis of each outcome in observational studies revealed clear heterogeneity (Table 1). For all outcomes considered in observational studies, the heterogeneity of effect could not be attributed to differences in sample size, country, statistical adjustment or year of enrolment of first patient: when stratifying analyses by these variables  $I^2$  remained high (eAppendix pg 10). Exclusion sensitivity analysis did not reduce heterogeneity amongst observational studies (eAppendix pg 34). Important confounders that were not adjusted for included severity of anaemia, bleeding, and volume of blood transfused, all key predictors of both transfusion and adverse outcome. We therefore attempted to assess each of these as potential sources of heterogeneity. Volume of RBC transfusion was most commonly reported across studies (Table 3). For MI and infection, heterogeneity was substantially reduced when analyses were stratified according to the number of RBC units transfused. Among the 8 studies that stratified their analyses by the number of RBC units transfused the association of MI and infection with transfusion increased with the number of RBC units transfused (Table 3). Dose-response relationships were estimable in three studies: a meta-analysis of these found an average increase in the odds of infection per unit of RBC administered of 1.20 (95% CI 1.13 – 1.28, eAppendix pg 20). Only 6 observational studies stratified their analyses based on preoperative or nadir haematocrit. Only 1 study adjusted for blood loss. Reporting of these analyses was inconsistent and therefore we were unable to conduct subgroup analyses based on these variables.

### **Discussion**



Our systematic review found that estimated effects of RBC transfusion differed markedly between cardiac surgical RCTs, non-cardiac surgical RCTs and observational studies. In RCTs of adult patients undergoing cardiac surgery, there was some evidence that a liberal RBC transfusion strategy reduced mortality compared with a restrictive transfusion strategy. There was no evidence of between-trial heterogeneity in results. However, fewer than 3400 patients have been randomised in such trials and only two included high-risk patients. In RCTs of more than 8000 non-cardiac surgical patients, there was little evidence that liberal transfusion reduced mortality compared to restrictive transfusion thresholds, and little evidence of between-trial heterogeneity in results. However, these trials included both adult and paediatric patients with different primary pathologies, as well as patients with important differences in comorbidities such as cardiovascular disease<sup>8</sup>. Stratifying analyses by cardiac disease state suggested that liberal transfusion strategies reduce mortality in RCTs exclusively recruiting patients with active or symptomatic cardiac disease, such as those undergoing cardiac surgery or experiencing myocardial infarction. Conversely, liberal transfusion strategies may increase mortality in RCTs recruiting patients without active or symptomatic cardiac disease.

By contrast with results from RCTs, observational studies of adult patients undergoing cardiac surgery reported substantially increased mortality, MI, pulmonary morbidity, AKI, CVA and infectious morbidity in those receiving RBC transfusion compared with those not transfused. However, there was substantial heterogeneity between the results of observational studies, and smaller studies tended to estimate the adverse effect of

RBC transfusion to be greater than larger studies. The adverse effect of RBC transfusion appeared to increase with increasing number of RBC units transfused.

The principal explanation for the divergence in our estimates of the risks and benefits of red cell transfusion between observational studies and RCTs in cardiac surgery is that the nature of comparisons, and groups being compared, differ between these types of studies. RCTs directly address the question of primary clinical interest by comparing transfusion thresholds that reflect the variability of contemporary clinical practice. They are the best way to evaluate the effect of transfusion on clinical outcomes, and have the least risk of bias. They achieve this by comparing outcomes in groups of patients that are similar because of randomisation, but who receive different frequencies and volumes of red cell transfusion. In these trials some patients in the liberal transfusion group do not receive a transfusion whereas some patients in the restrictive group do receive a transfusion, reproducing the effect of using different thresholds in clinical settings. Conversely, the observational studies compared transfusion with no transfusion. This is problematic because the substantial risk of death and other serious adverse events mean that it would not be ethically justified to consider no transfusion as a treatment policy in patients with severe bleeding or anaemia: transfusion can be lifesaving and no alternatives to transfusion are available in such patients. It follows that estimated effects of transfusion from observational studies are likely to have been subject to unmeasured confounding, because they included in the transfusion group patients who became so severely ill during surgery that they could never have remained transfusion free. The TRACS and TITRE2 trial investigators clearly demonstrated the potential for such bias. The intention to treat comparison in both trials showed no evidence of an adverse effect

of a liberal transfusion strategy <sup>21,25</sup>. However, a secondary multivariable logistic regression analysis of the data from both trials comparing patients who did and did not receive an RBC transfusion found that patients who received RBC transfusion were at higher risk of mortality: they were older, had higher Euroscores, longer CPB times, higher lactate values at the end of the operation, higher Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II scores and longer ITU and hospital stay compared to those who were not transfused <sup>76</sup>. Even after adjusting for these factors, receipt of transfusion was independently associated with an increase in adverse outcome and this apparent adverse effect increased with greater transfusion volume.

Two broad ways to address unmeasured confounding in observational studies could be considered. First, it might in principle be possible to precisely record the degree of morbidity present at the time of transfusion and measure such morbidity in non-transfused patients at an equivalent time. Propensity score methods could then be used to identify groups of patients whose probability of transfusion was close to 1 (or close to zero) and exclude them from analyses <sup>77</sup>. Second, observational analyses might mimic RCTs of liberal versus restrictive transfusion strategies, by following patients from the start of surgery and censoring those who depart from one or other strategy <sup>78</sup>. Such an approach was used to address the effect on mortality of commencing antiretroviral therapy at different CD4 count thresholds, in HIV-1 infected patients <sup>79</sup>. In practice, observational analyses of the effects of blood transfusion face considerable difficulties, even when appropriate analysis methods are used. For example, observational studies determine outcomes in patients from the time of exposure to the intervention i.e.

transfusion, and not the point of clinical decision making i.e. severe perioperative anaemia. This may produce a lead-time bias that exaggerates the effect by excluding clinical adverse events in patients who may have been severely anaemic, but were not initially transfused. In particular, it is extremely difficult to measure and control for all the factors influencing the decision to transfuse, since these vary during the operation and may be impossible to measure at times of emergency intervention. Importantly, none of the observational studies included in our review controlled for all the principal confounders, that is bleeding and anaemia. These findings lead us to question whether the results of existing observational studies should inform clinical transfusion decisions or blood management guidelines. Treatment guidelines are best informed by RCTs.

In RCTs of adult patients undergoing cardiac surgery, there was evidence that a liberal RBC transfusion strategy reduces mortality compared with a restrictive transfusion strategy. This however did not reach statistical significance. These apparent differences therefore could have arisen by chance: relatively few patients have been randomised in the context of cardiac surgery. Effects of transfusion estimated in RCTs may also be subject to bias. Studies were not blinded and, therefore decisions about perioperative care may have been affected by clinicians' knowledge of the randomised intervention ("performance bias"). Only three of the 6 cardiac surgical RCTs described the extent of adherence to the study protocol <sup>20,21,25</sup>. If transfusion thresholds in practice were more similar than specified in the protocol then differences between groups may have been attenuated. Nonetheless it is striking that the effects in four of the five cardiac surgical RCTs that reported on mortality were in the direction of benefit from liberal, compared with restrictive, transfusion thresholds. This is in contrast to RCTs in non-cardiac

surgical populations, which found no difference between liberal and restrictive transfusion strategies but instead a trend towards increased mortality with liberal transfusion. A survival benefit with more liberal transfusion is plausible; patients undergoing cardiac surgery, who are at the limits of their cardiovascular reserve preoperatively, and who frequently develop oxygen supply dependency postoperatively may benefit from higher haemoglobin levels to improve oxygen delivery. Our post hoc analysis that stratified RCTs into patients with or without active cardiac disease further supports this hypothesis.

Though subject to the limitations described above, our meta-analysis of RCTs represents the best available evidence that RBC transfusion may be safe (compared with available alternatives) in adult cardiac surgery, although the best threshold (in terms of severity of bleeding or anaemia) remains to be defined and may vary for different patient groups or stages of the perioperative journey<sup>80-82</sup>. Importantly, no RCT has shown that transfusion in these patients should be withheld until haemoglobin thresholds of 6-7g/dL (except in patients with evidence of critical end-organ ischemia), as per current guidelines<sup>4,5</sup>.

RBC transfusion rates range from 25-90% of patients across centres in contemporary studies<sup>13,83</sup>. This is largely because appropriate indications for the use of this costly and valuable resource are unknown. Such uncertainty with respect to an expensive pharmacological intervention would be unthinkable. The results of RCTs in non-cardiac surgery patients may not be transferrable to a population with symptomatic cardiac disease and it is of concern that these, as well as the results of observational studies, which we have concluded are unable to guide transfusion practice, form the basis of

national and international blood conservation guidelines <sup>4,5,84</sup>. Such guidelines urge clinicians to adopt restrictive transfusion practices due to the adverse outcomes demonstrated in these studies <sup>4,5</sup>. Reduction of this uncertainty requires adequately powered and well conducted RCTs that anticipate the limitations that we have described: they should include patients at high-risk of transfusion (for example by using validated transfusion risk scores), and document measures taken to ensure that other aspects of care are the same across intervention groups, for example by blinding surgeons and anaesthetists to treatment allocation and allowing other staff to make transfusion decisions according to the study protocol. The feasibility of large trials enrolling high-risk patients has been demonstrated in the TITRE2 trial<sup>25</sup> and other patient groups, such as gastrointestinal haemorrhage<sup>27</sup> and high risk patients following hip surgery<sup>8</sup>.

Author Contributions: NNP and GJM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: NNP, GJM.

Acquisition of data: VSA, NNP.

Analysis and interpretation of data: NNP, HEJ, BR, JACS, GJM.

Drafting of the manuscript: NNP, JACS, GJM.

Statistical analysis: NNP, HEJ, JACS.

Study supervision: GJM.

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## **Figure Legends**

**Figure 1.** Flow diagram of study selection.

**Figure 2.** Forest plot of the odds of mortality in RCTs stratified according to patient population.

**Figure 3.** Forest plot of the odds of mortality in observational studies.

**Table 1. Summary of results of meta-analyses estimating the effect of red blood cell transfusion, according to outcome and study design.**

<b>Outcome</b>	<b>Type of study</b>	<b>No. of studies / no. of patients</b>	<b>Fixed-effect OR (95% CI)</b>	<b>Fixed-effect P value</b>	<b>Random-effect OR (95% CI)</b>	<b>Random-effect P value</b>	<b>I<sup>2</sup>(%)</b>	<b>Heterogeneity P value</b>	<b>Egger test P value</b>
<b>Mortality</b>	Cardiac Surgical RCT	5/3304	0.70 (0.49–1.02)	0.06	0.70 (0.49–1.02)	0.06	0	0.46	0.80
	Non-Cardiac Surgical RCT	19/8341	1.10 (0.96–1.27)	0.16	1.07 (0.88–1.31)	0.49	29.7	0.11	0.41
	Observational	19/138357	1.48 (1.42–1.53)	<0.001	2.81 (2.21–3.56)	<0.001	95.4	<0.001	0.02
<b>Pulmonary</b>	Cardiac Surgical RCT	6/3357	0.94 (0.76–1.17)	0.58	0.94 (0.76–1.17)	0.58	0	0.51	0.66
	Non-Cardiac Surgical RCT	7/4944	1.15 (0.95–1.40)	0.14	1.15 (0.91–1.44)	0.25	17.6	0.30	0.90
	Observational	7/43431	1.68 (1.63–1.74)	<0.001	1.99 (1.47–2.69)	<0.001	97.0	<0.001	0.74
<b>AKI</b>	Cardiac Surgical RCT	5/3304	0.86 (0.68–1.09)	0.22	0.86 (0.68–1.09)	0.22	0	0.83	0.75
	Non-Cardiac Surgical RCT	2/1119	1.27 (0.95–1.69)	0.10	1.27 (0.95–1.69)	0.10	0	0.73	-
	Observational	14/59003	1.73 (1.65–1.83)	<0.001	3.06 (2.10–4.46)	<0.001	97.0	<0.001	0.08
<b>Infection</b>	Cardiac Surgical RCT	4/2802	0.97 (0.79–1.19)	0.75	0.97 (0.79–1.19)	0.75	0	0.69	0.21
	Non-Cardiac Surgical RCT	11/6225	1.16 (0.99–1.37)	0.07	1.16 (0.99–1.37)	0.07	0	0.45	0.48
	Observational	11/88025	1.81 (1.73–1.89)	<0.001	2.30 (1.85–2.86)	<0.001	72.9	<0.001	0.04
<b>MI</b>	Cardiac Surgical RCT	1/2003	1.34 (0.30- 6.02)	0.70	1.34 (0.30- 6.02)	0.70	-	-	-
	Non-Cardiac Surgical RCT	10/5539	0.79 (0.58–1.09)	0.15	0.88 (0.56–1.37)	0.57	25.8	0.21	0.11
	Observational	8/35763	1.55 (1.48–1.62)	<0.001	1.93 (1.45–2.58)	<0.001	89.1	<0.001	0.38
<b>CVA</b>	Cardiac Surgical RCT	1/2003	1.14 (0.57- 2.30)	0.71	1.14 (0.57- 2.30)	0.71	-	-	-
	Non-Cardiac Surgical RCT	8/3648	1.53 (0.83–2.83)	0.18	1.53 (0.83–2.83)	0.18	0	0.71	0.35
	Observational	7/43649	1.41 (1.34–1.48)	<0.001	2.03 (1.42–2.90)	<0.001	79.4	<0.001	0.08

**Table 2. Summary of meta-analyses in observational studies estimating the effect of red blood cell transfusion in adult cardiac surgery, stratified according to the quantity of RBC units transfused.**

<b>Outcome</b>	<b>No. of RBC Units</b>	<b>No. of studies</b>	<b>Random-effects OR (95% CI)</b>	<b>I<sup>2</sup>(%)</b>	<b>Heterogeneity P value</b>
<b>Mortality</b>	1-2 units	1	2.97 (0.96–9.20)	-	-
	3-6 units	1	5.82 (1.30–26.04)	-	-
	>6 units	3	3.84 (1.69–8.74)	43	0.17
<b>Pulmonary</b>	1-2 units	-	-	-	-
	3-6 units	-	-	-	-
	>6 units	-	-	-	-
<b>AKI</b>	1-2 units	2	3.45 (1.92–6.20)	86	0.01
	3-6 units	2	6.74 (3.68–12.33)	90	0.01
	>6 units	3	3.42 (2.35–4.97)	95	<0.001
<b>Infection</b>	1-2 units	4	1.73 (1.34–2.25)	0	0.64
	3-6 units	4	2.68 (1.49–4.82)	67	0.03
	>6 units	4	5.50 (2.62–11.53)	71	0.02
<b>MI</b>	1-2 units	2	2.22 (1.74 – 2.82)	62	0.11
	3-6 units	2	4.87 (3.80 – 6.24)	0	0.62
	>6 units	2	9.66 (7.49 – 12.46)	11	0.29
<b>CVA</b>	1-2 units	-	-	-	-
	3-6 units	-	-	-	-
	>6 units	-	-	-	-