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Risks of Restrictive Red Blood Cell Transfusion Strategies in Patients with Cardiovascular Disease (CVD): A Meta-analysis

Irene Cortés-Puch¹, Brandon M. Wiley², Junfeng Sun¹, Harvey G. Klein³, Judith Welsh⁴, Robert L. Danner¹, Peter Q. Eichacker¹, and Charles Natanson¹

¹Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD, USA

²Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

³Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, MD, USA

⁴National Institutes of Health Library, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Aim—To evaluate risks of restrictive red-blood cell transfusion strategies (hemoglobin 7–8 g/dL) in patients with and without known cardiovascular disease (CVD).

Background—Recent guidelines recommend restrictive strategies for CVD-patients hospitalized for non-CVD indications, patients without known CVD and patients hospitalized for CVD corrective procedures.

Methods/Materials—Database searches were conducted through December 2017 for randomized-clinical trials that enrolled patients with and without known CVD, hospitalized either for CVD corrective procedures or non-cardiac indications, comparing effects of liberal to restrictive strategies on major adverse coronary events (MACE) and death.

Results—In CVD patients not undergoing cardiac interventions, a liberal strategy decreased ($p=0.01$) the relative risk (95%CI) (RR) of MACE [0.50 (0.29–0.86)] ($I^2=0\%$). Among patients without known CVD, the incidence of MACE was lower (1.7 vs 3.9%), and the effect of a liberal strategy on MACE [0.79, (0.39–1.58)] was smaller and nonsignificant, but not different from CVD patients ($p=0.30$). Combining all CVD and non-CVD patients, a liberal strategy decreased MACE [0.59, (0.39–0.91); $p=0.02$]. Conversely, among studies reporting mortality, a liberal strategy decreased mortality in CVD patients (11.7% vs. 13.3%), but increased mortality (19.2% vs. 18.0%) in patients without known-CVD [interaction $p=0.05$; ratio of RR 0.73, (0.53–1.00)]. A liberal strategy also did not benefit patients undergoing cardiac surgery; data was insufficient for percutaneous cardiac procedures.

Conclusions—In patients hospitalized for non-cardiac indications, liberal transfusion strategies are associated with a decrease risk of MACE in both those with and without known CVD.

Corresponding Author: Charles Natanson, M.D., Critical Care Medicine Department, National Institutes of Health, 10 Center Drive, Room 2C145, Bethesda, MD 20892-1662, Tel: 301-496-9320, Fax: 301-402-1213, cnatanson@cc.nih.gov.

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However, this only provides a survival benefit to CVD-patients not admitted for CVD corrective procedures.

Keywords

Blood transfusion; Restrictive transfusion strategy; Liberal transfusion strategy; Cardiovascular disease; Transfusion trigger

INTRODUCTION

Two recently published guidelines from national associations including the AABB, formerly the American Association of Blood Banks (Carson *et al.* 2016), and the UK National Clinical Guideline Centre (NCGC) (Alexander *et al.* 2016), suggest that a restrictive red-blood cell (RBC) transfusion threshold of 7–8 g/dL for haemoglobin is safe in most clinical settings. In addition, the current AABB guidelines recommend a transfusion trigger of 8 g/dL for hospitalized patients with pre-existing cardiovascular disease (CVD), including those undergoing cardiac surgery. The AABB makes no recommendation for patients with acute coronary syndrome due to the lack of sufficient data from randomized clinical trials, whereas the NCGC recommends a threshold of 8 g/dL and a target value of 8–10 g/dL for this subset of patients.

Few trials of RBC transfusion triggers have focused on patients with underlying CVD. Most available data on transfusion practices for patients either with or without CVD, stem from decades-old retrospective analyses of large electronic medical record databases (Yang *et al.* 2005; Alexander *et al.* 2008; Salisbury *et al.* 2011; Salisbury *et al.* 2014; Sherwood *et al.* 2014; Magruder *et al.* 2017). These studies compare nadir haemoglobin or haematocrit values among transfused and non-transfused patients with CVD without identifying the specific transfusion thresholds or clinical indicators used to justify RBC transfusion (Alexander *et al.* 2008; Salisbury *et al.* 2011). The majority of studies do suggest that there is significant variability in transfusion practices among different centres (Hutton *et al.* 2005; Sherwood *et al.* 2014; Magruder *et al.* 2017). However, no trials have investigated whether the risks of restrictive or liberal strategies differ in patients with CVD compared to those without known CVD or how these risks compare in CVD patients hospitalized for cardiac corrective procedures *vs.* non-cardiac indications.

Two recent meta-analyses did summarize data evaluating transfusion thresholds in hospitalized patients with pre-existing CVD (Patel *et al.* 2015; Docherty *et al.* 2016). One study found a significantly increased incidence of myocardial infarction but not mortality associated with a restrictive transfusion threshold in known-CVD patients hospitalized for non-cardiac indications (Docherty *et al.* 2016). The other study reported no significant increase in mortality with a restrictive strategy among CVD patients undergoing cardiac corrective procedures (Patel *et al.* 2015). However, neither review directly addressed whether a restrictive strategy presents different risks in CVD compared to non-CVD patients, or directly compared whether these risks differ in CVD patients admitted for a corrective cardiac procedure (e.g. coronary surgery) *vs.* non-cardiac indications. These are important questions given that most guidelines still recommend restrictive RBC transfusion triggers for

all patients including those with or without known CVD and regardless of whether they are hospitalized for cardiac corrective procedures or not.

A single comprehensive analysis of the literature was performed to address these questions. We investigated whether the effects of restrictive or liberal transfusion policies on the incidence of myocardial infarction and acute coronary syndromes (major acute coronary events, MACE) (Hirji *et al.* 2017) and mortality in CVD patients admitted for non-cardiac reasons were similar (main effect) or significantly different (qualitative interaction) compared either to patients without known CVD or to CVD patients having cardiac corrective procedures.

MATERIALS AND METHODS

We included all published randomized clinical trials comparing restrictive and liberal transfusion triggers that provided data on patients with and without known CVD admitted for non-cardiac reasons and all published randomized clinical trials comparing the two transfusion strategies in CVD patients having cardiac corrective procedures. We further divided the cardiac corrective procedures into two types; patients having cardiac coronary surgery bypass grafts and/or valve surgery as one type; and those having percutaneous coronary interventions (PCI) as another. Trials were included if they enrolled and reported outcomes of patients with either known CAD (acute coronary syndrome or chronic ischemic heart disease) or other forms of CVD (including cardiac failure, valve disease and peripheral vascular disease). Major acute coronary events (MACE, myocardial infarction or acute coronary syndrome), and mortality rates were the selected end-points of interest.

Literature search and study selection

We searched PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials from database inception to December 31, 2017 without language restrictions for publications of randomized clinical trials comparing the use of a higher (liberal) and lower (restrictive) RBC transfusion trigger among adult patients with known CVD as well as without known CVD hospitalized for non-cardiac indications and those studies of CVD patients having corrective procedures either heart surgery or PCI. We also scanned the reference lists of analysed studies and references cited in reviews and guidelines identified in the searches.

To retrieve as much information as possible from all previous meta-analyses that included CVD patients, we requested from investigators any data regarding MACE or mortality not reported in the published studies (see S1 Supporting Information).

Statistical analysis

Risk ratios of mortality and MACE were analysed using random-effects models (DerSimonian *et al.* 1986), with 0.5 added to each cell in the studies with zero cells. Heterogeneity among studies was assessed using the Q statistic and I^2 value (Higgins *et al.* 2002).

For the included trials enrolling both patients with and without known CVD, in order to assess differences in treatment effects between these two patient groups (i.e., interaction), we used two methods to account for the correlation within each study: 1) a “one-step” approach with the study as a blocking factor; and 2) a “two-step” approach by first calculating the difference of log (RR) within each study, and then combining them using a standard random-effect model. These two methods gave almost identical results, so we only presented the latter for better visualization.

All analyses were performed using *R* version 3.4.3 (R Development Core Team, 2017). Traditional meta-analysis were performed using *R* packages *meta* version 4.9-0 (Schwarzer 2015) and *metafor* version 2.0-0 (Viechtbauer 2010). Two-sided p-values ≤ 0.05 were considered significant. The Bayesian meta-analysis was performed using *R* package *bmeta* version 0.1.2 (cran.r-project.org/web/packages/bmeta). We used RR with normal approximation. Random-effect models with non-informative priors were used.

RESULTS

Study characteristics

Fig. 1 shows a flowchart of study selection and enrolment. Seventeen randomized clinical trials met inclusion criteria. Nine included patients with and without known pre-existing CVD hospitalized for various non-cardiac indications [peripheral vascular surgery (Bush *et al.* 1997), critical care (Hebert *et al.* 1999; Walsh *et al.* 2013), orthopaedics (Carson *et al.* 2011; Parker 2013; Gregersen *et al.* 2015), septic shock (Holst *et al.* 2014), surgical oncology (de Almeida *et al.* 2015) and acute upper GI bleeding (Jairath *et al.* 2015)]. Six studies enrolled cardiac surgery patients (Bracey *et al.* 1999; Murphy *et al.* 2007; Hajjar *et al.* 2010; Shehata *et al.* 2012; Murphy *et al.* 2015; Mazer *et al.* 2017), two enrolled PCI patients (Cooper *et al.* 2011; Carson *et al.* 2013). Characteristics of the included studies are summarized in Table 1 and S1 Table. Patients were enrolled from July 1994 through March 2017. These seventeen studies enrolled from 45 to 5243 patients each, for a total of 14397 patients. Of these studies; nine provided data for 2048 patients with known CVD and 3337 without known CVD, all admitted for non-cardiac indications; six provided data for 7343 patients with CVD admitted for cardiac surgery; and two provided data for 154 patients with CVD admitted for PCI.

Overall mortality and MACE risk in patients with pre-existing CVD admitted for non-CVD indications

Nine trials provided data on the mortality endpoint. Among patients with known CVD hospitalized for non-CVD indications, there were 119 deaths among the 1032 CVD patients reported in the liberal transfusion group and 135 deaths among the 1016 CVD patients in the restrictive transfusion group (Fig. 2A). There was no evidence of significant heterogeneity between studies for the mortality endpoint ($I^2=2.8\%$, $p=0.41$). Overall, a liberal compared to a restrictive transfusion strategy produced a nominally but not statistically significant decreased relative risk of mortality (95%CI) in known CVD patients hospitalized for non-CVD indications [0.90 (0.72–1.12), $p=0.33$].

Four of the nine studies provided data on the MACE endpoint in these known CVD patients admitted for non-CVD indications. MACE occurred in 19 of 729 CVD patients in the liberal transfusion group and 39 of 745 CVD patients in the restrictive transfusion group (Fig. 2B). There was no evidence of heterogeneity across individual studies for the MACE endpoint ($I^2=0\%$, $p=0.91$). A liberal compared to restrictive transfusion strategy was associated with a significantly decreased risk of MACE [0.50, (0.29–0.86), $p=0.01$] among all patients with known pre-existing CVD hospitalized for non-CVD indications.

Subgroup analyses

Based on significant findings for MACE, we performed a sensitivity analysis to determine the consistency of the risk for both MACE and mortality across studies using lower and higher restrictive transfusion triggers. Fig. 3 shows mortality and MACE endpoints when the restrictive transfusion trigger was less than 8 g/ (~7 g/dL) or 8 g/dL or greater (~ 8 g/dL) in CVD patients. The decreased risk of mortality across the studies comparing a liberal trigger vs. a restrictive trigger of ~ 7 g/dL [0.87 (0.68–1.12), $I^2=0\%$], and across studies comparing a liberal trigger vs. a restrictive trigger of ~ 8 g/dL [0.83 (0.49–1.42), $I^2=23\%$], were each not statistically significant, but were both similar to the overall decrease [0.90 (0.72–1.12)] (Fig. 3A). The decreased risk of MACE in pre-existing CVD patients across the studies comparing a liberal trigger vs. a restrictive transfusion trigger of ~7 g/dL [0.38 (0.09–1.53), $I^2=0\%$] and across the studies comparing a liberal vs. a restrictive trigger of ~ 8 g/dL [0.53 (0.30–0.94)] was significant only for the latter ($p=0.03$), but both were similar to the overall decrease [0.50 (0.29–0.86), $I^2=0\%$] (Fig. 3B).

Comparing MACE and mortality risks in patients with pre-existing CVD to those without known CVD

For these studies, we next compared the overall relative risk of a liberal vs. restrictive transfusion strategy on the primary endpoints of MACE reported in four of the nine trials and death reported in all nine trials among patients with pre-existing CVD compared to those without known CVD. A liberal compared to a restrictive transfusion strategy reduced the relative risk of MACE in patients both with known CVD [2.6% versus 5.2%; 0.50, (0.29–0.86)] and without known CVD (1.5% versus 1.9%; 0.79, (0.39–1.58) in beneficial patterns that were similar ($p=0.30$ for interaction, Fig. 4B). In fact, the relative decreases in risk of MACE using a liberal rather than a restrictive strategy in patients with vs. without known CVD were remarkably alike (RR 0.50 vs. 0.79 respectively) and had 95% confidence intervals that almost completely overlapped [CI (0.29–0.86) vs. (0.39–1.58) respectively]. As expected, the absolute incidence of MACE among hospitalized patients managed with a restrictive strategy was much greater in those with pre-existing CVD compared to those without known CVD (5.2% vs. 1.9% absolute incidence of MACE, respectively). However, a similar relative decrease in MACE was found employing a liberal strategy, despite these unsurprising differences in the absolute incidence of MACE. When examined over all patients from these four studies, whether they had known or unknown pre-existing CVD, a liberal compared to a restrictive transfusion strategy was associated with a significant decrease in MACE [0.59 (0.39–0.91), $p=0.02$].

Conversely, among the nine studies reporting on the mortality endpoint separately for patients with and without known pre-existing CVD and hospitalized for non-cardiac indications, the overall effect of a liberal strategy on mortality was significantly different and opposite depending on whether patients had known CVD or not ($p=0.05$, qualitative interaction) (Fig. 4A, S1 Fig). In patients randomized to a liberal strategy, mortality rates were lower among those with known pre-existing CVD (11.7% vs. 13.3%, respectively), but higher in those without known CVD (19.2% vs. 18.0%, respectively). The ratio (95% CI) of the relative risks of death with a liberal strategy in patients with compared to those without known CVD was significant [0.73 (0.53–1.00), $p=0.05$]. This divergent effect of a liberal strategy on mortality in patient with and without known CVD is at odds with its directionally similar effects on MACE.

MACE and mortality risks comparing patients with CVD hospitalized for non-cardiac indications versus cardiac corrective procedures including either cardiac surgery or PCI

The effect of a liberal vs. restrictive transfusion strategy on mortality was not statistically significantly different ($p=0.26$, interaction) in patients with CVD hospitalized for non-cardiac indications compared to those hospitalized for cardiac corrective procedures including either PCI or cardiac surgery (Fig. 5B). The relative risk of death was not statistically significantly decreased with a liberal strategy in patients with known CVD hospitalized for non-cardiac reasons [0.90 (0.73–1.11), $p=0.32$] or for those having either PCI [0.26 (0.06–1.22), $p=0.09$] or cardiac surgery [0.96 (0.74–1.24), $p=0.73$]. Overall though, among the 17 studies providing data for patients with CVD hospitalized for non-cardiac indications and for cardiac corrective procedures, a liberal strategy was associated with a nominal decrease in death that was not statistically significant [0.91 (0.77–1.07), $p=0.25$].

There was a quantitative interaction for the effect of a liberal transfusion strategy on MACE comparing these three different CVD groups ($p=0.08$ for interaction) that appeared ordered and prevented averaging over them (Fig. 5). Specifically, a liberal strategy decreased the relative risk of MACE significantly in patients with CVD hospitalized for non-cardiac indications [0.50 (0.29–0.86), $p=0.01$] and nominally in those with CVD having PCI [0.66, (0.24–1.83) $p=0.42$], but not at all in those with CVD having cardiac surgery [0.98 (0.76–1.24), $p=0.84$].

Bayesian analysis

The posterior estimate of RR for mortality (liberal vs restrictive transfusion strategy) is 0.85 with 95% Credible Interval (CrI) (0.56, 1.18), with an 83% posterior probability of the liberal strategy being better. The posterior estimate of RR for myocardial infarction (liberal vs restrictive) is 0.47 with 95% CrI (0.02, 9.87), with an 84% posterior probability of the liberal strategy being better.

DISCUSSION

Seventeen randomized clinical trials enrolling 14,397 hospitalized patients provided data for 12,882 patients on the primary endpoints examined here, either for patients with and without

known CVD hospitalized for non-cardiac indications or for CVD patients hospitalized for cardiac corrective procedures. Four trials enrolled patients with pre-existing CVD hospitalized for non-cardiac reasons and provided MACE data. Among the 1474 patients included, a liberal transfusion trigger was associated with a 50% decrease in the risk of MACE. This effect was consistent independent of whether a restrictive threshold of ~ 7 g/dL or ~ 8 g/dL of haemoglobin was studied. This effect was also similar ($I^2=0\%$, $P=0.91$) for these patients regardless of the setting (critical care, orthopaedics, septic shock, and surgical oncology). These four trials also included patients without known underlying CVD and among these 1853 patients, a liberal transfusion strategy similarly decreased the relative risk of MACE. In addition to these four trials of non-cardiac hospital settings, we found six trials including CVD patients hospitalized for corrective cardiac procedures including either PCI (two trials) or cardiac surgery (four trials). When comparing the effect of a liberal transfusion strategy in CVD patients between trials of non-cardiac hospitalizations and those for corrective cardiac procedures, the benefit on MACE was statistically significant for non-cardiac settings, but only nominally so for PCI patients and not at all significant for cardiac corrective surgery patients. Correcting the CVD abnormality with PCI or surgery may decrease or nullify the benefit of a liberal transfusion strategy on MACE during any hospitalization.

Overall, in nine trials including 1949 patients with pre-existing CVD hospitalized for non-cardiac indications compared to 3337 admitted without known CVD, the effect of a liberal transfusion trigger on mortality was significantly different and opposite ($p=0.05$, qualitative interaction). A liberal transfusion trigger increased mortality in patients without known CVD, but decreased mortality in those with pre-existing CVD. To explain these unexpected and opposite effects on mortality, it seems likely that some additional and independent adverse survival effect of a liberal strategy was predominately affecting patients without known CVD. This adverse effect was sufficient to reverse the potential beneficial effect on mortality expected from decreasing MACE. These findings are consistent with results from the Transfusion in Critical Care trial (TRICC) for mortality in patients with and without severe cardiovascular disease managed with either a liberal or restrictive strategy (Hebert *et al.* 2001; Deans *et al.* 2007). In the TRICC trial, younger and healthier patients who were less likely to have CVD and would not normally be transfused during usual care, had the greatest fold increase in mortality in the liberal *versus* the restrictive arm. Lastly, comparing patients with CVD hospitalized for non-cardiac indications *vs.* cardiac interventions, a liberal strategy had a nominally beneficial effect on mortality rates but this difference was not statistically significant.

Two studies in this meta-analysis had a combined weight of over 70% here. One was a large multi-centre transfusion trigger trial, enrolling more than 2000 orthopaedic surgery patients (Carson *et al.* 2011). One of the most rigorously conducted studies to date using this methodology, this trial found a significant increase after 30-days in the incidence of MACE among orthopaedic patients with CVD and treated with a restrictive strategy (J. Carson, personal communication). The second publication (Mazer *et al.* 2017) studied more than 5000 cardiac surgery patients and found that higher transfusion triggers were not associated with meaningful differences in the risks of MACE and mortality. Taken together, these data support the notion that for patients with chronic CVD requiring hospitalization for a serious

non-cardiac problem, the risk of MACE may be reduced by maintaining haemoglobin levels > 9.5 g/dL. In contrast, if a CVD patient is admitted for correction of a cardiovascular abnormality with surgery, maintaining higher haemoglobin levels does not appear to be beneficial. Determining with any certainty whether there is any benefit to a liberal strategy during less invasive cardiac corrective procedures such as PCI is hampered by insufficient data. There were only two trials enrolling 155 patients providing data on this question. However, one of these trials showed a significant increase in mortality with a restrictive strategy (Carson 2013).

We recognize limitations to the interpretation of these data. We excluded trials not specifying inclusion of patients with CVD and trials in which requests for data on CVD patients were made but not provided or not available. This could have led to unrecognized selection bias. As discussed above, after the enrolment period of studies for our meta-analysis ended, a very large cardiac surgery trial studying transfusion triggers in over 5000 patients was published (Mazer *et al.* 2017). Due to the influential nature of this trial, we reopened enrolment until December of 2017 with another search. Thus, this analysis is not prospective but retrospective. Other limitations include the following. The specific transfusion thresholds and the definitions of CVD and acute coronary syndrome varied between studies. Even though effect sizes were determined within trials first and combined effects determined, this may have had unrecognized consequences. Some of the outcomes analysed from specific trials were not primary or pre-specified endpoints. Also, some of the subgroups examined were not prospectively stratified in trials and were not part of an original randomization scheme. Therefore, the data analysed here should be considered hypothesis-generating, rather than definitive. However, the importance of these data rests less on the definitive nature of the individual findings than on their consistency.

In patients both with and without known pre-existing CVD and admitted for non-cardiac indications in these studies, the decrease in the relative risk of MACE with a liberal *vs.* a restrictive strategy was similar across different reasons for hospitalization and regardless of whether a restrictive strategy used a haemoglobin threshold of 7 or 8 g/dL. Moreover, the overall point estimates we examined were always on the side of increased mortality and MACE rates for a restrictive transfusion trigger regardless of whether the patient was admitted for non-cardiac reasons, PCI or cardiac surgery, although the benefit was minimal or non-existent for mortality and MACE in patients hospitalized for cardiac surgery. From 17 trials, we obtained 26 individual estimates in this analysis for risk of death and MACE with a restrictive *versus* liberal transfusion strategy (see Fig. 5). Of these 26 estimates, 21 favoured a liberal strategy, and five a restrictive strategy. No study to date has found a restrictive transfusion strategy to be significantly beneficial in CVD patients and at least two studies (Carson *et al.* 2011 and 2013) and one other meta-analysis (Docherty *et al.* 2016) found that a liberal strategy was significantly beneficial in CVD patients not undergoing cardiac surgery.

To determine probabilities for the significant adverse effect of a restrictive strategy on MACE in patients with pre-existing CVD hospitalized for non-cardiac indications, we performed a Bayesian analysis. The probability that a restrictive strategy is worse than a liberal one was 84% for MACE and 83% for mortality. These findings are based on nine

studies enrolling thousands of patients with and without known CVD. Likewise, a recent meta-analysis of transfusion trigger trials examining older hospitalized patients (>65 years old) likely to be at increased risk for CVD reported a significant increase in 30 and 90-day mortality with a restrictive transfusion strategy (Simon *et al.* 2017). Nevertheless, an appropriately designed prospective, large multicentre transfusion trial of patients with known pre-existing CVD or at high risk for CVD and admitted for non-cardiac procedures would be needed to provide definitive evidence and determine best transfusion practices. Risks in such a study could be minimized by enrolling only patients cared for by physicians who currently approve of and/or use a restrictive RBC transfusion strategy in CVD patients, or by including only centres with policies mandating restrictive strategies in CVD patients.

The present study supports transfusion guidelines that recommend restrictive rather than liberal transfusion strategies for CVD patients undergoing cardiac corrective procedures. There are insufficient data to make such a recommendation for less invasive cardiac procedures such as PCI. In contrast, for hospitalized patients admitted for non-cardiac reasons with pre-existing CVD or at high risk for CVD, clinicians should be reluctant to adopt restrictive transfusion strategies until prospective studies provide additional information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
PRISMA flow diagram

A. Mortality Risk **B. Major Acute Coronary Event**

Fig. 2. Forest plots of relative risks for mortality and major acute coronary events (MACE, myocardial infarction and acute coronary syndrome) in patients with pre-existing cardiovascular disease hospitalized for non-cardiac indications

The relative risk (RR) (closed diamonds, liberal *versus* restrictive) and 95% confidence interval (CI) (horizontal bars) are plotted for each individual trial included in the analysis for mortality (upper panel) and MACE (lower panel).

A. Mortality Risk **B. Acute Coronary Events**

Fig. 3. Sensitivity analysis - Forest plots of relative risks for mortality and MACE for subgroups of patients with pre-existing cardiovascular disease hospitalized for non-cardiac indications

The relative risk (RR) (closed diamonds, liberal *versus* restrictive) and 95% confidence interval (CI) (horizontal bars) are plotted for each individual trial included in the analysis for mortality (upper panel) and acute coronary events (lower panel) for two subgroups: the studies employing a restrictive transfusion trigger of < 8 g/dL (left panels), and the studies employing a restrictive transfusion trigger of 8g/dL or greater (right panels).

A. Mortality Risk

* Restrictive vs. liberal transfusion triggers had significantly different and opposite effect on mortality depending on the presence or absence of known cardiovascular disease (CVD). In patients with known CVD, liberal strategies *decreased* mortality, and in patients without CVD disease, liberal strategies *increased* mortality.

B. Major Acute Coronary Event

** In patients with known cardiovascular disease (CVD) as well as in those without known CV disease, there was a *decrease* in acute coronary events with a liberal transfusion strategy that overall was statistically significant.

Fig. 4. Combined mortality and MACE rates for enrolled patients with and without pre-existing cardiovascular disease hospitalized for non-cardiac indications

The combined percentage rate for mortality (left panel) and MACE (right panel) in patients with (closed circles) and without (open circles) cardiovascular disease are plotted here for a liberal and restrictive strategy (x axis) from the eight trials providing mortality data and four trials providing MACE data on enrolled patients with and without cardiovascular disease.

Fig. 5. Combined mortality and MACE rates for cardiovascular disease patients hospitalized for non-cardiac indications, or percutaneous cardiac corrective procedures or cardiac surgery
The combined overall relative risk for mortality (left panels) and MACE (right panels) in patients with cardiovascular disease are plotted here for a liberal vs. restrictive strategy for cardiovascular disease patients hospitalized for cardiac surgery (top panels), or percutaneous cardiac corrective procedures (middle panels) or non-cardiac indications (bottom panels).

Table 1

Characteristics of included studies

Study	Year	Cardiac Disease	Classification	Setting	Enrolled Patients	Years of Enrolment	Transfusion Triggers	Mortality		Major Acute Coronary Events	
								Restrictive	Liberal	Restrictive	Liberal
CARDIOVASCULAR DISEASE PATIENTS HOSPITALIZED FOR NON-CARDIAC REASONS											
Bush	1997	Chronic	Vascular Surgery	Elective Aortic or infrainguinal arterial reconstruction	99 randomised - all CVD	August 1995– November 1996	Hb = 9 g/dL vs 10 g/dL	7/50	4/49	N/A	N/A
Hebert	1999	Chronic	Critical Care	Mixed ICU	838 randomised - 257 CVD / 581 non-CVD	November 1994 – November 1997	Hb = 7 g/dL vs 10 g/dL	29/111	31/146	N/A	N/A
Carson	2011	Chronic	Orthopaedics	Hip Surgery	2016 randomised - 1268CVD / 748 non-CVD	July 2004 – February 2009	Hb = 8 g/dL vs 10 g/dL	32/624	40/628	32/631	17/636
Parker	2013	Chronic	Orthopaedics	Hip Surgery	200 randomised - 87 CVD / 113 non-CVD	August 2002 – May 2012	Hb = 8 g/dL vs 10 g/dL	3/34	2/24	N/A	N/A
Walsh	2013	Chronic	Critical Care	Mixed ICU	100 randomised - 32 CVD / 68 non-CVD	August 2009 – December 2010	Hb = 7 g/dL vs 9 g/dL	3/17	4/15	1/17	0/15
Holst	2014	Chronic	Septic Shock	Septic Shock	1005 randomised - 141 CVD / 857 non-CVD	December 2011 – December 2013	Hb = 7 g/dL vs 9 g/dL	42/75	33/66	6/75	2/66
Gregersen	2015	Chronic	Orthopaedics	Hip Surgery	284 randomised - 59 CVD / 225 non-CVD	January 2010 – June 2013	Hb = 9.7 g/dL vs 11.3 g/dL	6/34	3/25	N/A	N/A
de Almeida	2015	Chronic	Surgical Oncology	Surgical Oncology	198 randomised - 34 CVD / 163 non-CVD	January 2012 – July 2012	Hb = 7 g/dL vs 9 g/dL	7/22	0/12	0/22	0/12
Jairath	2015	Chronic	Acute Upper GI bleeding	Acute Upper GI bleeding	936 enrolled - 176 CVD / 760 non-CVD	September 2012 – March 2013	Hb = 8 g/dL vs 10 g/dL	6/49	2/67	N/A	N/A
CARDIAC SURGERY PATIENTS											
Bracey	1999	Acute	Cardiac Surgery	CABG	437 randomised	February 1997 – November 1997	Hb = 8g/dL vs physician orders (9 g/dL by protocol)	3/215	6/222	1/212	0/216
Murphy	2007	Acute	Cardiac Surgery	CABG and/or valve	321 randomised	September 2005 – October 2006	Hb = 7g/dL vs 8 g/dL	5/162	3/159	N/A	N/A
Hajjar	2010	Acute	Cardiac Surgery	CABG	512 randomised	February 2009 – February 2010	HTC = 24% vs 30%	15/249	13/253	N/A	N/A
Shehata	2012	Acute	Cardiac Surgery	CABG and/or valve	50 randomised	January 2007 – June 2010	Hb = 7–7.5 g/dL vs 9.5–10 g/dL	4/25	1/25	1/25	0/25
Murphy	2015	Acute	Cardiac Surgery or Vascular Surgery	CABG and/or valve or Major Aortic Procedure	2003 randomised	July 2009 – February 2013	Hb = 7.5 g/dL vs 9 g/dL	26/1000	19/1003	3/987	4/981
Mazer	2017	Acute	Cardiac Surgery	CABG and/or valve	5243 randomised – 827 excluded *	January 2014 – March 2017	Hb < 7.5g/dL vs < 9.5g/dL	61/1994	68/2036	117/1994	117/2036

Study	Year	Cardiac Disease	Classification	Setting	Enrolled Patients	Years of Enrolment	Transfusion Triggers	Mortality		Major Acute Coronary Events	
								Restrictive	Liberal	Restrictive	Liberal
PERCUTANEOUS CORONARY INTERVENTION PATIENTS											
Cooper	2011	Acute	PCI	ACS or stable angina	45 randomised	May 2003 – October 2009	HTC = 24% vs 30%	2/24	1/21	1/24	0/21
Carson	2013	Acute	PCI	ACS	110 randomised	March 2010 – May 2012	Hb = 8 g/dL vs 10 g/dL	7/54	1/55	7/54	5/55

* other “non-CABG category”, contained non-prespecified groups such as myxoma surgery