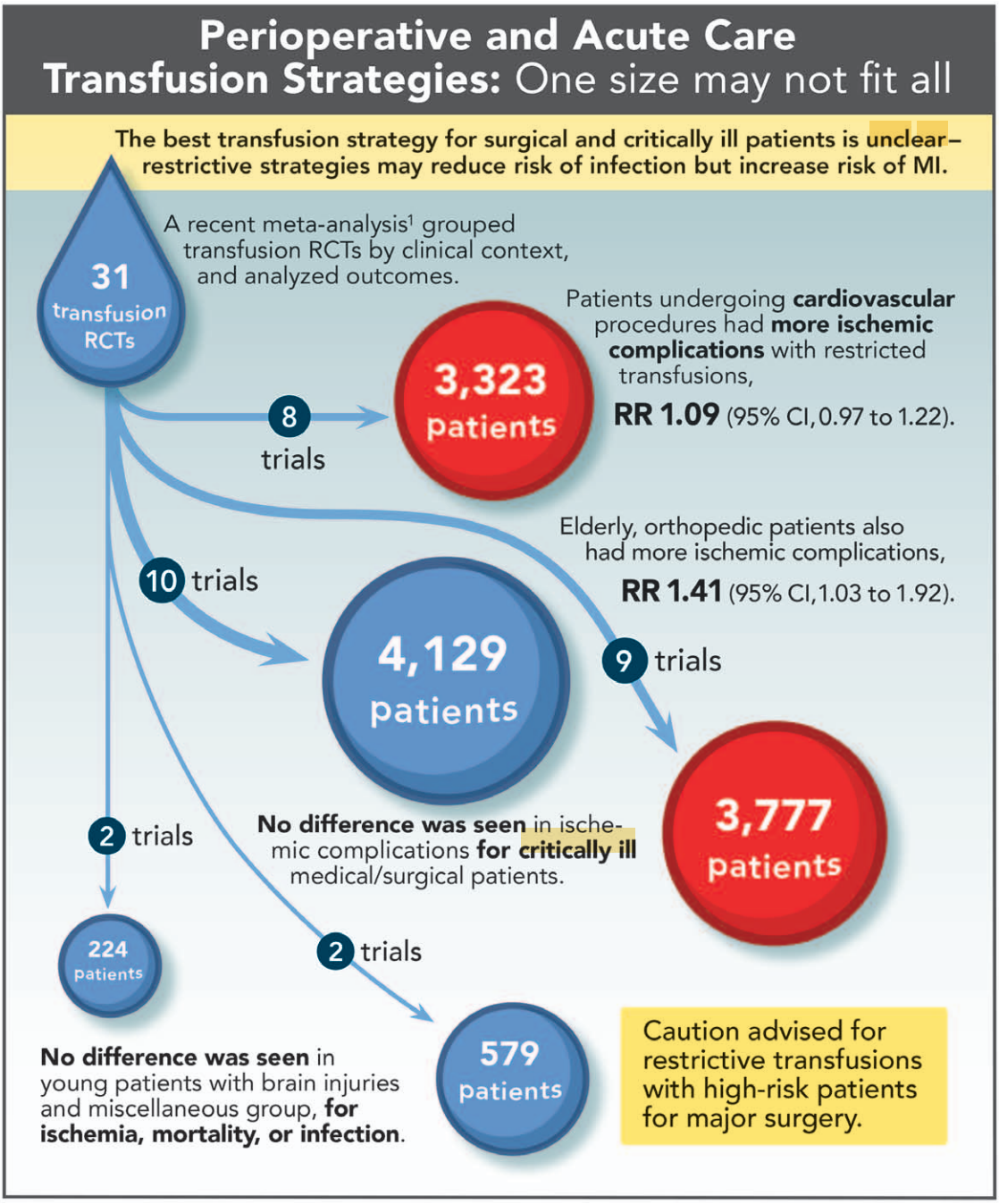
ANESTHESIOLOGY



MI = myocardial injury; RCT = randomized, controlled trial; RR = relative risk.

Infographic created by Jonathan P. Wanderer, Vanderbilt University School of Medicine, and James P. Rathmell, Brigham and Women's Health Care/Harvard Medical School. Illustration by Annemarie Johnson, Vivo Visuals. Dr. Wanderer is funded by the Foundation for Anesthesia Education and Research, Schaumburg, Illinois, and Anesthesia Quality Institute's Mentored Research Training Grant—Health Services Research, Schaumburg, Illinois. Address correspondence to Dr. Wanderer: jon.wanderer@vanderbilt.edu.

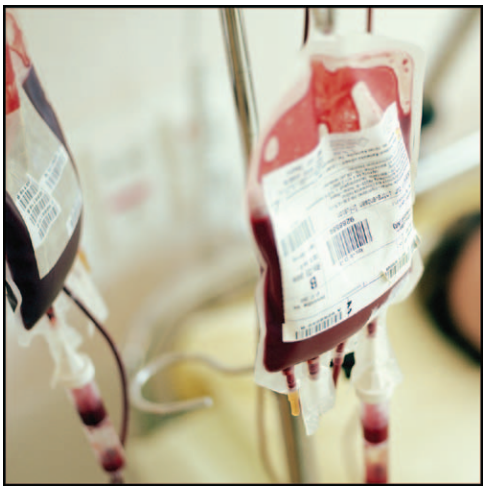
1. Hovaguimian F, Myles PS: Restrictive *versus* liberal transfusion strategy in the perioperative and acute care settings: A context-specific systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2016; 125:46–61

Approaching a Safe Last Resort

Triggers for Perioperative Blood Transfusion

W. Scott Beattie, M.D., Ph.D., F.R.C.P.C., Duminda N. Wijeysundera, M.D., Ph.D., F.R.C.P.C.

ANESTHESIOLOGISTS and perioperative physicians often face the challenging decision between transfusing or not transfusing an anemic patient. This decision implicitly requires balancing the risks of anemia *versus* the risks of red cell transfusion in an individual patient. Anemia affects more than 30% of patients undergoing elective surgery, and is associated with increased perioperative morbidity and mortality.[1,2] Conversely, the risks of perioperative red cell transfusion are also well described.[3,4] Observational studies have found that administration of just 1 to 2 units of erythrocyte concentrate to surgical patients is associated with increased morbidity and mortality. Nonetheless, it must be acknowledged that observational studies will likely never be able to adequately adjust for the inherent confounding by indication associated with perioperative transfusion. Stated otherwise, clinicians preferentially transfuse patients who are undergoing extensive risky surgery or have more severe comorbidity, especially cardiovascular disease. These confounders are almost always inadequately captured in observational datasets, therefore precluding adequate risk adjustment when assessing the association between transfusion and outcomes.



"[There are] context-specific differences in appropriate transfusion triggers...[and this research] provides important guidance on how best to transfuse anemic surgical patients."

Given the clinical importance of identifying appropriate circumstances to transfuse anemic surgical patients and the limitations of observational research methods to address this question, current "best evidence" comes from so-called "transfusion trigger trials." In these randomized controlled trials, patients are randomized to have either a high hemoglobin concentration threshold for triggering a transfusion (*i.e.*, "liberal" transfusion strategy) or a low hemoglobin concentration threshold (*i.e.*, "restrictive" transfusion strategy).

While widely viewed as considerably less biased than equivalent observational studies, the transfusion trigger study design has been criticized.[5] For example, these trials cannot be blinded and typically lack a control group representing usual clinical practice. The definition of "restrictive" and "liberal" across trials has been heterogeneous. Most importantly, the design entails imposing fixed standardized thresholds to *all* patients within an arm of the trial. By comparison, in clinical practice, physicians individualize a patient's transfusion threshold based on concomitant comorbidity. Thus, most perioperative physicians would specify different transfusion triggers for an otherwise healthy 35-yr-old patient compared to a 65-yr-old individual with longstanding cardiovascular disease.[6] Subgroup-specific differences in the efficacy and safety of transfusion trigger thresholds are both physiologically plausible and consistent with physicians' usual clinical practice.

In this issue of ANESTHESIOLOGY, Hovaguimian and Myles[7] present a meta-analysis of previous transfusion trigger trials that seeks to account for these important context-specific differences in appropriate transfusion triggers. While several previous meta-analyses of transfusion trigger trials have been published,[8–11] the study by Hovaguimian and Myles is superior in several important respects. *First*, they included every trial evaluating two transfusion thresholds in patients more than 18 yr of age. *Second*, they evaluated the compliance to the transfusion protocol, the erythrocyte-sparing effect, and the absolute difference in hemoglobin concentrations achieved between study arms. *Third*, these analyses evaluated outcomes separately within five *a priori* defined "context-specific" strata chosen to minimize the patient and procedural heterogeneity.

The results are important, and point to the importance of considering context when determining an appropriate transfusion trigger. In the younger noncardiac population, it is clear that a restrictive strategy (transfusion when hemoglobin concentration decreases below 70 g/l) is superior. In our view, this should be the policy *for this population*. Conversely, application of a restrictive strategy (transfusion when

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Corresponding article on page 46.

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hemoglobin concentration decreases below 80 g/l) during cardiovascular surgery did not increase ischemic events or infections, but was associated with a disturbing trend toward increased mortality. Ongoing studies, such as the Transfusion Requirements in Cardiac Surgery III trial (Clinicaltrials.gov NCT 02042898), will better inform any policies with respect to appropriate transfusion triggers in cardiac surgery.

Finally, in noncardiac surgery, a restrictive strategy (transfusion when hemoglobin concentration decreases below 80 g/l) increased ischemic events, but surprisingly did not affect the mortality rate. The current guidelines in this patient population are largely based on, and consistent with, the restrictive transfusion strategy employed in the Functional Outcomes in Cardiovascular Patients Undergoing Hip Fracture Repair trial.[12] In this randomized controlled trial comparing transfusion triggers in high cardiac risk, predominately elderly female, patients after hip fracture surgery, the restrictive transfusion threshold was 80 g/l. Importantly, the Functional Outcomes in Cardiovascular Patients Undergoing Hip Fracture Repair trial incorporated a provision to transfuse at any time if there were "symptoms." Notably, the trial found that rapid bleeding, heart failure, hypotension, and tachycardia occurred frequently and more often in the restrictive strategy arm. But when these hemodynamic symptoms were treated, there were no differences in postoperative myocardial injury or deaths at either 30 days or 3 yr.[13] Thus, on the basis of this trial at least, a practice of administering erythrocyte concentrate when the hemoglobin concentration decreases to 80 g/l with the provision for earlier symptomatic transfusion appears both safe and economical. Whether this treatment plan is generalizable to other populations requires further study.

While the study by Hovaguimian and Myles provides important guidance on how best to transfuse anemic surgical patients, transfusion is just one component of a comprehensive strategy to mitigate the perioperative risks of anemia. There is a critical need to study preoperative interventions, such as iron and erythropoietin, to potentially reduce preoperative anemia.[14] In addition, an overall strategy must incorporate methods for minimizing perioperative blood loss, such as appropriate fluid administration protocols, protocols for managing long-term preoperative anticoagulants[15] or antiplatelet agents,[16] appropriate thromboprophylaxis regimens,[17] maintenance of normothermia,[18] targeted use of antifibrinolytics,[19] and careful surgical technique. In this scheme, transfusion is considered the "last resort" in anemia management, further restricting exposure to the risks of blood products.

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, Khreiss M, Dahdaleh FS, Khavandi K, Sfeir PM, Soweid A, Hoballah JJ, Taher AT, Jamali FR: Preoperative anaemia and postoperative outcomes in noncardiac surgery: A retrospective cohort study. Lancet 2011; 378:1396–407
2. Beattie WS, Karkouti K, Wijeysundera DN, Tait G: Risk associated with preoperative anemia in noncardiac surgery: A single-center cohort study. Anesthesiology 2009; 110:574–81
3. Carson JL, Duff A, Berlin JA, Lawrence VA, Poses RM, Huber EC, O'Hara DA, Noveck H, Strom BL: Perioperative blood transfusion and postoperative mortality. JAMA 1998; 279:199–205
4. Karkouti K, Stukel TA, Beattie WS, Elsaadany S, Li P, Berger R, Wijeysundera DN: Relationship of erythrocyte transfusion with short- and long-term mortality in a population-based surgical cohort. Anesthesiology 2012; 117:1175–83
5. Deans KJ, Minneci PC, Danner RL, Eichacker PQ, Natanson C: Practice misalignments in randomized controlled trials: Identification, impact, and potential solutions. Anesth Analg 2010; 111:444–50
6. Hébert PC, Wells G, Martin C, Tweeddale M, Marshall J, Blajchman M, Pagliarello G, Schweitzer I, Calder L: A Canadian survey of transfusion practices in critically ill patients. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. Crit Care Med 1998; 26:482–7
7. Hovaguimian F, Myles PS: Restrictive *versus* liberal transfusion strategy in the perioperative and acute care settings: A context-specific systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2016; 125: 46–61
8. Carson JL, Carless PA, Hebert PC: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2012; 4:CD002042
9. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JA, Murphy GJ: Indications for red blood cell transfusion in cardiac surgery: A systematic review and meta-analysis. Lancet Haematol 2015; 2:e543–53
10. Fominskiy E, Putzu A, Monaco F, Scandroglio AM, Karaskov A, Galas FR, Hajjar LA, Zangrillo A, Landoni G: Liberal transfusion strategy improves survival in perioperative but not in critically ill patients. A meta-analysis of randomised trials. Br J Anaesth 2015; 115:511–9
11. Docherty AB, O'Donnell R, Brunskill S, Trivella M, Doree C, Holst L, Parker M, Gregersen M, Pinheiro de Almeida J, Walsh TS, Stanworth SJ: Effect of restrictive *versus* liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: Systematic review and meta-analysis. BMJ 2016; 352:i1351
12. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J; FOCUS Investigators: Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453–62
13. Carson JL, Sieber F, Cook DR, Hoover DR, Noveck H, Chaitman BR, Fleisher L, Beaupre L, Macaulay W, Rhoads

GG, Paris B, Zagorin A, Sanders DW, Zakriya KJ, Magaziner J: Liberal *versus* restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. Lancet 2015; 385:1183–9

14. Hogan M, Klein AA, Richards T: The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery. Eur J Cardiothorac Surg 2015; 47:218–26
15. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL; BRIDGE Investigators: Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015; 373:823–33
16. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S; POISE-2 Investigators: Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014; 370:1494–503
17. Sharfman ZT, Campbell JC, Mirocha JM, Spitzer AI: Balancing thromboprophylaxis and bleeding in total joint arthroplasty: Impact of eliminating enoxaparin and predonation and implementing pneumatic compression and tranexamic acid. J Arthroplasty 2015; 10.1016/j.arth.2015.11.046
18. Rajagopalan S, Mascha E, Na J, Sessler DI: The effects of mild perioperative hypothermia on blood loss and transfusion requirement. Anesthesiology 2008; 108:71–7
19. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011; 16:CD001886

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Choleric Temperamental Education for 1893 Classes by "Masters of Anaesthesia"

Flemish artist Maerten de Vos' spear-wielding *Cholericus* (1583) reminds us that a **fire**-like patient of "choleric" temperament commanded the hot, dry "yellow bile" humor linked by ancient Greeks with elemental **fire**. By 1893 at Chicago's Post-Graduate School of Anaesthesia (PGSA), professors were tutoring future "Master of the Science of Anaesthesia" candidates to anticipate that a choleric patient's anesthesia might comprise—what today's anesthesiologists would characterize as—(1) a swift induction, (2) a risk for heart-depressing anesthetic overdosage (termed "concussion" by the PGSA), and (3) a stormy emergence. PGSA founder and secretary, Professor Samuel J. Hayes, D.D.S., M.S.A., taught that choleric patients might resist preanesthetic calming. Dr. Hayes also used the journal that he edited, *The Dental and Surgical Microcosm*, as a primer for teaching PGSA students about the dangers of cardiovascular "concussion" from anesthetic overdose.

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Restrictive *versus* Liberal Transfusion Strategy in the Perioperative and Acute Care Settings

A Context-specific Systematic Review and Meta-analysis of Randomized Controlled Trials

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Paul S. Myles, M.B.B.S., M.P.H., M.D., F.C.A.I., F.A.N.Z.C.A., F.R.C.A., F.A.H.M.S.

ABSTRACT

Background: Blood transfusions are associated with morbidity and mortality. However, restrictive thresholds could harm patients less able to tolerate anemia. Using a *context-specific* approach (according to patient characteristics and clinical settings), the authors conducted a systematic review to quantify the effects of transfusion strategies.

Methods: The authors searched MEDLINE, EMBASE, CENTRAL, and grey literature sources to November 2015 for randomized controlled trials comparing restrictive *versus* liberal transfusion strategies applied more than 24 h in adult surgical or critically ill patients. Data were independently extracted. Risk ratios were calculated for 30-day complications, defined as inadequate oxygen supply (myocardial, cerebral, renal, mesenteric, and peripheral ischemic injury; arrhythmia; and unstable angina), mortality, composite of both, and infections. Statistical combination followed a *context-specific* approach. Additional analyses explored transfusion protocol heterogeneity and cointerventions effects.

Results: Thirty-one trials were regrouped into five *context-specific* risk strata. In patients undergoing cardiac/vascular procedures, restrictive strategies seemed to increase the risk of events reflecting inadequate oxygen supply (risk ratio [RR], 1.09; 95% CI, 0.97 to 1.22), mortality (RR, 1.39; 95% CI, 0.95 to 2.04), and composite events (RR, 1.12; 95% CI, 1.01 to 1.24—3322, 3245, and 3322 patients, respectively). Similar results were found in elderly orthopedic patients (inadequate oxygen supply: RR, 1.41; 95% CI, 1.03 to 1.92; mortality: RR, 1.09; 95% CI, 0.80 to 1.49; composite outcome: RR, 1.24; 95% CI, 1.00 to 1.54—3465, 3546, and 3749 patients, respectively), but not in critically ill patients. No difference was found for infections, although a protective effect may exist. Risk estimates varied with successful/unsuccessful transfusion protocol implementation.

Conclusions: Restrictive transfusion strategies should be applied with caution in high-risk patients undergoing major surgery.
(Anesthesiology 2016; 125:46-61)

DESPITE studies suggesting unfavorable outcomes after the administration of erythrocytes,[1–5] the optimal transfusion strategy in surgical and critically ill patients remains unclear. Concerns have been raised about harmful effects of low hemoglobin transfusion thresholds in individuals less able to tolerate anemia, such as the elderly and patients with cardiovascular disease or cancer.[6–9] Previously published meta-analyses were inconclusive: minimizing exposure to allogeneic blood reduced the risk of infection, but patients assigned to these restrictive transfusion strategies seemed also at a higher risk of myocardial infarction (MI).[10,11]

Since variability among studies is inevitable, undertaking meta-analyses generally entails some degree of heterogeneity, of which three different subtypes have been described[12]: (1) *clinical heterogeneity*, which results from variability in participants, interventions, or outcomes; (2) *methodologic heterogeneity*, a consequence of variability in study design and risk of bias; (3) *statistical heterogeneity*,

What We Already Know about This Topic

- Although many studies and some systematic reviews have examined the role of transfusion strategies in patient morbidity and mortality, these have not included the role for context-specific (patient characteristics and clinical setting) conditions

What This Article Tells Us That Is New

- In a review of 31 trials grouped into 5 context-specific strata, restrictive transfusion strategies increased the risk of mortality and composite morbidity in patients undergoing cardiac/vascular procedures and in elderly orthopedic patients

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 11. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. James C. Eisenach, M.D., served as Editor-in-Chief for this article.

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which results from clinical or methodologic heterogeneity, or both. Identifying and addressing each type of heterogeneity remains a key step in undertaking meta-analyses. To date, however, most systematic reviews on transfusion strategies failed to address *clinical heterogeneity*, thereby limiting their interpretation.[13–16]

Therefore, we conducted a *context-specific* systematic review and meta-analysis of randomized controlled trials (RCTs) investigating the effects of restrictive transfusion strategies in the perioperative and acute care settings. The rationale for a *contextual* approach (*i.e.*, stratification of the analysis according to patient characteristics and clinical settings) was based on the prespecified assumption that a high degree of clinical heterogeneity may hinder the identification of group-specific effects: pooling data from various patient populations (young and elderly patients, for instance) or from various settings (such as cardiac surgery and postpartum setting) may result in a dilution of the intervention effects. Since clinical diversity may also result from variability in study interventions, we were also interested in the effects of different transfusion protocols and in the contributing role of cointerventions (*i.e.*, administration of non-erythrocyte blood products, hemostatic agents, or intravenous fluids) in complication rates.

Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] Eligibility criteria, outcomes, and methods of analysis were prespecified (study protocol available at: http://alfredanaesthesia.org.au/research).

Eligibility Criteria

Only fully published reports of RCTs were included. For duplicates or follow-up or ancillary studies, the first published article was considered the main study.[18] Crossover designs or studies not adequately controlled were excluded. Trials evaluating a multiinterventional protocol were excluded if the effect of transfusion strategies could not be distinguished from the effect of other interventions. Cluster randomized trials were included only if methods of analysis allowed for clustering.[19]

Only trials conducted among adult patients (more than 18 yr old) in the perioperative, emergency, or intensive care settings were considered. We excluded studies conducted in patients with sickle cell disease.

We searched for studies comparing two different laboratory values (or using symptoms of anemia) to guide erythrocyte administration. We excluded studies applying transfusion strategies 24 h or less, trials using a hemodilution protocol, and interventions relying on preoperative autologous blood donation, since some effects (such as immunomodulation) were unlikely to develop,[20] and this approach is no longer recommended.[21]

We were interested in studies reporting events associated with, or worsened by, anemia.[5,22–28] To fully capture all the effects of transfusion strategies,[29,30] individual outcome events were combined into the following categories: "inadequate oxygen supply" (myocardial, cerebral, renal, mesenteric, and peripheral ischemic injury; arrhythmia; unstable angina), "mortality," and a composite category "inadequate oxygen supply + mortality" (see description provided in Supplemental Digital Content 1, http://links.lww.com/ALN/B275, which describes outcome categories). Only events occurring within 30 days were retrieved because substantial hemoglobin recovery seems to occur within 2 months after surgery/intensive care unit stay.[31,32] Our aim was also to explore the immunomodulatory effects of allogeneic blood: since transfusions have been associated with impaired host defenses,[33,34] we searched for studies reporting new infections occurring within 30 days.

Data Sources and Searches

We performed a systematic electronic search in the MEDLINE (Ovid), EMBASE (Ovid), and Cochrane CENTRAL databases. Both MeSH terms and keywords combined with Boolean operators were used (see strategy provided in Supplemental Digital Content 2, http://links.lww.com/ALN/B276, which provides the full search strategy used in this systematic review). The following sources of grey literature were screened: OpenGrey, International Clinical Trials Registry Platform, ClinicalTrials.gov. Additional reports were identified by hand-searching bibliographies. No language or date restrictions were applied. The last electronic search was done on November 17, 2015.

Study Selection

Titles and abstracts were assessed for eligibility by two independent reviewers (Drs. Hovaguimian and Myles). Duplicate publications were identified through comparison of reports for author names, enrolment date, setting, intervention, participant number, or baseline data. Disagreements were resolved through discussion.

Data Extraction

Data were extracted from original reports by one reviewer (Dr. Hovaguimian) and entered in a form specifically designed for this review (see description provided in Supplemental Digital Content 3, http://links.lww.com/ALN/B277, which details which information was extracted). The second reviewer (Dr. Myles) verified these data, and queries were resolved through discussion. Missing, unclear, or incomplete data in the original report were clarified by contacting authors (two provided additional data).[35,36] Outcome data were not considered for analysis if no clarification could be obtained. Data from duplicates were extracted and merged under a unique study identification name. Data were subsequently entered into the Cochrane Review Manager software (RevMan, version 5.3.3—The Cochrane Collaboration, The

Nordic Cochrane Centre, Denmark, 2014) by one reviewer (Dr. Hovaguimian) and checked by the second reviewer (Dr. Myles).

Risk of Bias in Individual Studies

The risk of bias was assessed using the Cochrane "Risk of bias" tool, which evaluates randomization method, concealment of treatment allocation, blinding of participants and personnel, blinding of outcome assessor, risk of incomplete outcome data, risk of selective reporting, and other sources of bias (ethics approval, informed consent, funding, and conflict of interest).[37] Each item was rated at "low," "unclear," or "high" risk of bias. The effects of detection and attrition bias were specifically explored, since this may affect studies evaluating adverse events (AEs).[38] For cluster randomized trials, we used specific items as recommended elsewhere.[19] Disagreements were resolved through discussion.

Measures of Effect, Data Handling, and Transformation

Dichotomous outcomes were reported as risk ratios with 95% CIs, while continuous data were expressed as weighted mean differences with 95% CI. All statistical analyses were performed with the Cochrane Review Manager software. Data handling and transformation were necessary for some endpoints. Composite outcome categories were obtained by combining individual outcome data, as performed in previous reports (see description provided in Supplemental Digital Content 4, http://links.lww.com/ALN/B278, which outlines data handling, transformation, and combination).[10,13]

Data Synthesis and Analysis

Differences between studies in terms of patient characteristics and/or clinical settings (*i.e.*, clinical diversity) may affect effect estimates.[12] To control for these sources of heterogeneity, we used a prespecified *context-specific* approach and stratified the analysis by (1) patient-specific risk of developing complications (according to age, comorbidities, and concomitant medication); (2) setting-related risk of complications (type of surgery). Studies conducted in similar populations and settings were regrouped into *risk strata* (see description provided in Supplemental Digital Content 5, http://links.lww.com/ALN/B279, which explains the rationale and methods used for strata generation). Meta-analyses were performed only if data were obtained from at least two studies.

To assess if our context-specific approach was sensible, we conducted for each outcome category a nonstratified analysis (*i.e.*, data pooling without controlling for clinical diversity) and performed a test of interaction using the Cochran Q and Higgins I^2. We considered that different population parameters were represented within each risk stratum when the Cochran Q *P*-value was less than 0.05 or when I^2 was greater than 50%.[12,39] When data combination was deemed inappropriate, a qualitative assessment was performed.

Statistical heterogeneity was assessed by visual inspection of forest plots and by using the chi-square test and the I^2 statistic. When data were heterogeneous ($P < 0.1$, I^2 greater than 50%), we searched for methodologic sources of heterogeneity.[12] We used a fixed-effect model, unless overt clinical or residual statistical heterogeneity was present (see fig., Supplemental Digital Content 6, http://links.lww.com/ALN/B280, which outlines how heterogeneity assessment was performed).[39,40]

Additional Analyses

Effect of "Successful Studies." We assumed that only studies demonstrating successful transfusion protocol implementation would reflect true intervention effects. Success was arbitrarily defined as a statistically significant difference between transfusion groups in two performance indicators: (1) hemoglobin levels over time *and* (2) mean erythrocyte units/group. *P* values were assessed from original reports. We also explored other possible determinants of success, such as hemoglobin thresholds, transfusion-sparing effect, and adherence rates (see description provided in Supplemental Digital Content 7, http://links.lww.com/ALN/B281, which outlines which indicators were used to assess successful protocol implementation).

Effect of "Cointerventions." Several routinely administered drugs or other management measures may participate in the occurrence of AE. Thus, we assessed the effects of nonerythrocyte blood products (cryoprecipitate, fresh frozen plasma, and platelets), antifibrinolytics, clotting factor concentrates, and fluids administration.

Results

Study Selection

We identified 4,684 records from MEDLINE, 858 records from EMBASE, and 1741 records from CENTRAL (fig. 1). Other sources retrieved no additional records. Of these 7,283 records, 7,193 were excluded after preliminary screening. Of the 90 remaining reports, 53 were discarded because the study population was ineligible, the intervention was inappropriate, the design was problematic, or the study presented other issues (see description provided in Supplemental Digital Content 8, http://links.lww.com/ALN/B282, which lists excluded studies). Of 37 relevant reports, 6 were excluded after more thorough examination: 2 were duplicate publications, 1 was a preliminary analysis, and 3 were ancillary or follow-up studies of included studies.[41–46] Thus, we included 31 RCTs comparing restrictive with liberal transfusion strategies in the perioperative or acute care setting.[6–9,35,36,47–71]

Study Characteristics

Study Design, Participants, and Setting (table 1). Included studies were published between 1956 and 2015, and all were reported in the English language. A two-arm parallel design

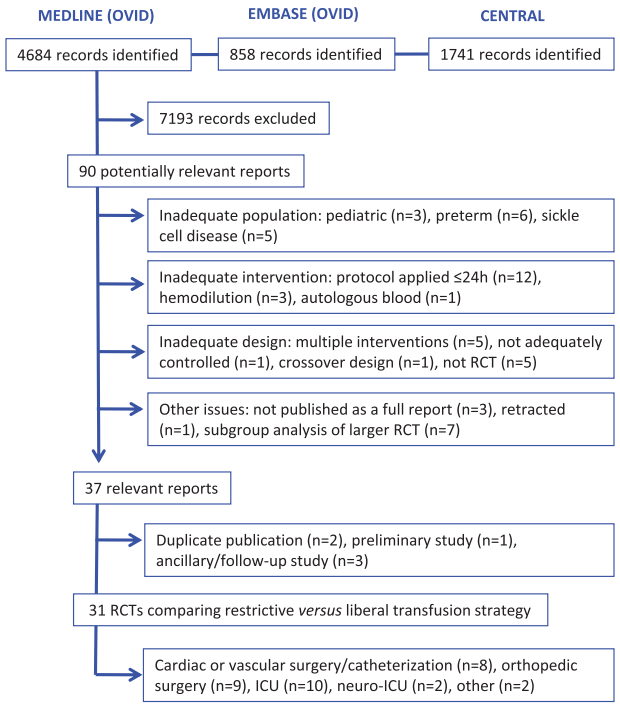

Fig. 1. Flow diagram illustrating the study selection process. ICU = intensive care unit; RCT = randomized controlled trial.

was used in all trials except in a factorial 2 × 2 design investigating transfusion strategies and erythropoietin administration.[65] One study was a cluster randomized trial.[35]

Trials with similar patient populations and clinical settings were regrouped into five risk strata: (1) patients with cardiovascular disease undergoing cardiac or vascular procedures (surgery or catheterization—8 trials, 3,323 patients)[6,47,48,51,55,60,66,67]; (2) elderly population with varying cardiovascular disease undergoing orthopedic surgery (9 trials, 3,777 patients)[8,9,49,50,52,54,62,63,68]; (3) mixed surgical and medical patients with varying comorbidities admitted to an acute care facility (emergency or intensive care unit—10 trials, 4,129 patients)[7,35,36,53,56–59,69,70]; (4) younger, less comorbid population admitted for acute traumatic brain injury or subarachnoid hemorrhage (2 trials, 244 patients)[61,65]; (5) other patients or settings: one conducted among anemic women in the postpartum phase and one including thrombocytopenic middle-aged patients with hematologic cancer (2 trials, 579 patients).[64,71]

Intervention: Transfusion Protocol (table 2). In the first group, four studies failed in implementing their protocol: in two, the absolute difference in hemoglobin thresholds was only 10 g/l, the transfusion-sparing effect was less than 20%, and nonadherence rates in the restrictive group were more than or equal to 15%;[47,48] in one, transfusion thresholds were higher in some patients of the restrictive group compared to liberal[67]; in one, nonadherence rates, transfusion-sparing effects, and transfusion thresholds seemed adequate, but the sample size was small.[51]

In group 2, data to assess success were lacking in one trial,[63] and three studies showed unsuccessful implementation: in one, the transfusion-sparing effect was less than 20%, and nonadherence rates in the restrictive group were more than or equal to 15%[62]; in one, the lack of standardized protocol in the liberal group resulted in a negative transfusion-sparing effect[68]; and in one, surgical procedures were not adequately balanced between groups (liberal patients were more likely to bleed).[8]

In group 3, success was unclear in two studies ("mean erythrocyte units" were reported *per transfused patients* instead of *per strategy group*).[7,53] In one unsuccessful study, the transfusion-sparing effect was less than 20%, and nonadherence rates in the liberal group were more than or equal to 15%.[35]

Group 4 included two studies that demonstrated successful implementation but the protocols were heterogeneous: one study used particularly high thresholds (restrictive: hemoglobin 100 g/l; liberal: hemoglobin 115 g/l), while the other compared 70 with 100 g/l.[61,65]

In the last group, success was unclear in one study reporting negligible transfusion-sparing effects and high nonadherence rates in the restrictive group.[71]

Risk of Bias in Included Studies

The risk of selection bias was deemed low in only 7 of 31 included studies (see fig., Supplemental Digital Content 9, http://links.lww.com/ALN/B283, which summarizes the risk of bias in included studies).[7,56,58,66,68,70,71] All studies were at high or unclear risk of performance bias. Outcome assessors were blinded in 13 studies.[6–8,36,49,50,54,55,58,60,61,65,71] The risk of attrition bias was low in all studies except three: in two,[54,67] it was not possible to assess if attrition was balanced between groups, and in one,[64] attrition rates exceeded 20%. The risk of selective reporting was low in all studies, but in one trial, study findings were reported in three different publications without mention of other existing reports.[9,41,42]

Results of Individual Studies and Data Syntheses

Events Associated to or Worsened by Anemia.

Inadequate Oxygen Supply. (See fig., Supplemental Digital Content 10, http://links.lww.com/ALN/B284, which illustrates the risk of events reflecting inadequate oxygen supply.) In group 1, early MI was reported in seven studies, arrhythmia in five, angina in two, stroke or transient ischemic attack (TIA) in five, acute kidney injury in five, and mesenteric ischemia in one (see table, Supplemental Digital Content 11, http://links.lww.com/ALN/B285, which outlines outcome reporting across studies). In one study, stroke/TIA was reported in combination with delirium and could not be extracted.[55] Thus, data from 8 studies (3,322 patients) were combined[6,47,48,51,55,60,66,67]: in patients with cardiovascular disease assigned to a restrictive strategy and undergoing high-risk surgery, there was a possible increase in events reflecting inadequate oxygen supply (risk ratio [RR], 1.09; 95% CI, 0.97 to 1.22).

In group 2, early MI was reported in five studies, arrhythmia in three, stroke/TIA in five, and AKI in two (see table,

Table 1. Summary of Included Studies

Study Characteristics				Patient Characteristics					
					Mean Age (yr)		Particular Medication n (%)		
Study ID	Design	Total Participants (n)	Setting or Reason for Admission	Particular Population	Restrictive	Liberal	Name	Restrictive	Liberal
Group 1: CV disease, cardiac/vascular surgery or interventional catheterization									
Bracey *et al.*, 1999[47]	Two-arm RCT	428	Elective cardiac (CABG)	No comorbidities reported	61	62	Aspirin	151 (71)	147 (68)
							Oral AC	4 (2)	4 (2)
							Other anti-PLT	11 (5)	11 (5)
Bush *et al.*, 1997[48]	Two-arm RCT	99	Elective vascular (aortic + infrainguinal)	Variety of CV diseases	66	64		NR	
Carson *et al.*, 2013[6]	Two-arm RCT	110	Interventional catheterization	Variety of CV diseases, hemoglobin < 100 g/l	74	67	Aspirin	48 (87)	51 (93)
							Other anti-PLT	44 (80)	45 (82)
							Chronic AC	0	4 (7)
Cooper *et al.*, 2011[51]	Two-arm RCT	45	Interventional catheterization or cardiac surgery	Variety of CV diseases, hematocrit < 30%	70	76	Aspirin	24 (100)	21 (100)
							Other anti-PLT	21 (88)	17 (81)
							Heparin	10 (41)	7 (33)
							Gp antagonist	2 (8)	1 (5)
Hajjar *et al.*, 2010[55]	Two-arm RCT	502	Elective cardiac (CABG, valve)	Variety of CV diseases; low-risk of bleeding*	59	61	Aspirin	94 (38)	103 (41)
Murphy *et al.*, 2015[60]	Two-arm RCT	2003	Elective cardiac (CABG, valve, aortic)	Variety of CV diseases; low-risk of bleeding*	70	71	Aspirin	277 (28)	284 (28)
							Other anti-PLT	41 (4.1)	37 (3.7)
Shehata *et al.*, 2012[66]	Two-arm RCT	50	Elective cardiac (CABG, valve)	High risk of transfusion†	67	69	Other anti-PLT	18 (72)	17 (68)
							Oral AC	7 (28)	8 (32)
Slight *et al.*, 2008[67]	Two-arm RCT	86	Elective cardiac (CABG, valve)	Variety of CV diseases	65	66		NR	
Group 2: Elderly, orthopedic surgery									
Carson *et al.*, 1998[49]	Two-arm RCT	84	Hip fracture	Mostly ASA III with CV disease (45% IHD), mostly community dwelling	83	81	Aspirin	12 (28.6)	15 (35.7)
							Chronic AC	14 (33.3)	15 (35.7)
Carson *et al.*, 2011[50]	Two-arm RCT	2016	Hip fracture	Mostly ASA III with CV disease (40% IHD), mostly community dwelling	82	82		NR	
Fan *et al.*, 2014[52]	Two-arm RCT	186	Elective lower limb joint replacement (hip)	Mostly ASA II, some with CV disease (only 10% IHD)	73	75		NR	
Foss *et al.*, 2009[8]	Two-arm RCT	120	Hip fracture	Mostly ASA III with CV disease (12% IHD), community dwelling	81	81		NR	
Gregersen *et al.*, 2015[9]	Two-arm RCT	284	Hip fracture	21% with CV disease, nursing home or sheltered housing	86	87	Iron supplement	123 (88)	118 (87)
Grover *et al.*, 2006[54]	Two-arm RCT	218	Elective lower limb joint replacement	Some with CV disease (only 12% IHD)	71	72		NR	
Nielsen *et al.*, 2014[62]	Two-arm RCT	66	Elective hip revision	Mostly ASA II, only NYHA I	68	72		NR	
Parker, 2013[63]	Two-arm RCT	200	Hip fracture	Mostly ASA III with CV disease (only 15% IHD), community dwelling	84	84		NR	
So-Osman *et al.*, 2010[68]	Two-arm RCT	603	Elective lower limb joint replacement	Mostly "high-risk" patients‡	71	70	No significant difference for NSAID and AC. No values reported.		

(*Continued*)

Table 1. (Continued)

Study Characteristics				Patient Characteristics					
					Mean Age (yr)		Particular Medication n (%)		
Study ID	Design	Total Participants (n)	Setting or Reason for Admission	Particular Population	Restrictive	Liberal	Name	Restrictive	Liberal
Group 3: Mixed medical/surgical cases, acute care									
de Almeida *et al*., 2015[7]	Two-arm RCT	198	Surveillance postmajor abdominal surgery	Low risk of bleeding*; some with CV disease (7% IHD)	64	64		NR	
Fortune *et al*., 1987[53]	Two-arm RCT	25	Trauma or surgical bleeding	Hemorrhagic shock class III or IV, all intubated; no history of MI	47	47		NR	
Hébert *et al*., 1995[57]	Two-arm RCT	69	Various diagnoses	Mixed surgical and medical population with hemoglobin < 90 g/l; some with CV disease	59	59		NR	
Hébert *et al*., 1999[56]	Two-arm RCT	838	Various diagnoses	Mixed surgical and medical population with hemoglobin < 90 g/l	57	58		NR	
Holst *et al*., 2014[58]	Two-arm RCT	1,000	Septic shock	Mixed surgical and medical population with hemoglobin < 90 g/l; some with CV disease	67	67		NR	
Jairath *et al*., 2015[35]	Two-arm cluster RCT	6 clusters, 936 patients	Upper-GI bleeding	No exsanguinating bleeding; some with CV disease (15% IHD)	58	60	Iron supplement LMWH	43 (11) 9 (2)	47 (9) 5 (1)
Markatou *et al*., 2012[59]	Two-arm RCT	52	Surveillance postmajor abdominal surgery	Low risk of bleeding*	58	63		NR	
Topley and Fisher, 1956[69]	Two-arm RCT	22	Trauma	Actively bleeding, no elderly patient	NR	NR		NR	
Villanueva *et al*., 2013[70]	Two-arm RCT	889	Upper-GI bleeding	Excluded if exsanguinating bleeding or major cardiovascular disease	59	59	Chronic AC	47 (11)	60 (13.5)
Walsh *et al*., 2013[36]	Two-arm RCT	100	Various diagnoses	Mixed surgical and medical population with hemoglobin < 90 g/l, mechanically ventilated; some with CV disease (32% IHD)	67	68		NR	
Group 4: Younger, fitter, brain injury/intracranial bleeding									
Naidech *et al*., 2010[61]	Two-arm RCT	44	Neuro-ICU	Subarachnoid hemorrhage, some with CV disease	59	54		NR	
Robertson *et al*., 2014[65]	Factorial 2 × 2	200	Neuro-ICU	Closed traumatic brain injury, GCS motor ≤ 5, no major chronic disease or AC	28	31	Iron supplement EPO	99 (100) 49 (50)	101 (100) 53 (52)
Group 5: Other patients and settings									
Prick *et al*., 2014[64]	Two-arm RCT	519	Postpartum hemorrhage	Hemodynamically stable ASA I women with hemoglobin 48–79 g/l; some had surgery	31	31		NR	
Webert *et al*., 2008[71]	Two-arm RCT	60	Hematooncology	Thrombocytopenic patients, no IHD in past 6 months, no coagulation disorders	51	45		NR	

*Patients with thrombocytopenia, coagulopathy, or chronic anticoagulation (AC) therapy were excluded. †Risk assessment based on comorbidities and complexity of surgery (as reported in the original article). ‡Defined as nonsinus rhythm, unstable ischemic heart disease (IHD), or myocardial infarction (MI) < 6 mo, heart failure, valvular disease, age > 70 yr, peripheral artery disease, large vessel surgery, stroke/transient ischemic attack, left ventricular hypertrophy (electrocardiogram/transthoracic echocardiography), chronic pulmonary disease with polyglobulism, and insulin-dependent diabetes mellitus.

Anti-PLT = antiplatelet therapy; ASA = American Society of Anesthesiologists (score); CABG = coronary artery bypass graft; CV = cardiovascular; EPO = erythropoietin; GCS = Glasgow Coma Scale; GI = gastrointestinal; Gp = glycoprotein; ICU = intensive care unit; LMWH = low-molecular-weight heparin; NR = not reported; NSAID = nonsteroidal antiinflammatory drugs; NYHA = New York Heart Association classification; RCT = randomized controlled trial.

Table 2. Transfusion Protocols Across Studies

Study Characteristics		Intervention Characteristics														
		Hemoglobin Threshold (g/l)			Not Exposed to Allogeneic Blood (%)			Nonadherence* (%)		Success					Mean Storage Time (d)	
Study ID	Setting or Reason for Admission	Restrictive	Liberal	Δ	Restrictive	Liberal	Δ	Restrictive	Liberal	Mean Erythrocyte UI Differed Significantly between Groups?	Hemoglobin Levels Differed Significantly over Time?	Protocol Application	Follow-up	Type of Erythrocyte (Leukoreduction, Volume, Mean Hematocrit)	Restrictive	Liberal
Group 1: CV disease, cardiac/vascular surgery or interventional catheterization																
Bracey *et al.*, 1999[47]	Elective cardiac (CABG)	80	90	**10**	65	52	**13**	**15**	**16**	Yes	No	POP	Discharge	NR	NR	NR
Bush *et al.*, 1997[48]	Elective vascular (aortic + infrainguinal)	90	100	**10**	20	12	**8**	**20**	**NR**	No	Yes	IOP + POP	Discharge	NR	NR	NR
Carson *et al.*, 2013[6]	Interventional catheterization	S (80)	100	20	73	6	67	2	7	Yes	Yes	Hospital stay (maximum 30 d)	6 mo	Mainly LeukoR	23	25
Cooper *et al.*, 2011[51]	Interventional catheteriza-tion or cardiac surgery	*80*	*100*	20	46	0	46	4	5	No	Yes	Discharge	30 d	NR	NR	NR
Hajjar *et al.*, 2010[55]	Elective cardiac (CABG, valve)	*80*	*100*	20	70	36	34	2	0	Yes	Yes	IOP + POP (ICU only)	30 d	Non-LeukoR, 250–320 ml, hematocrit 80%	3	3
Murphy *et al.*, 2015[60]	Elective cardiac (CABG, valve, aortic)	75	90	15	47	8	39	10	6	Yes	Yes	POP	3 mo	NR	NR	NR
Shehata *et al.*, 2012[66]	Elective cardiac (CABG, valve)	70 IOP, 75 POP	95 IOP, 100 POP	25	48	12	36	NA	NA	Yes	Yes	IOP + POP	Discharge	NR	NR	NR
Slight *et al.*, 2008[67]	Elective cardiac (CABG, valve)	RCV schema	80–90	**NA**	67	47	20	9	5	Yes	No	POP (48 h only)	3 mo	NR	NR	NR
Group 2: Elderly, orthopedic surgery																
Carson *et al.*, 1998[49]	Hip fracture	S (80)	100	(20)	55	2	53	10	2	Yes	Yes	POP	60 d	NR	NR	NR
Carson *et al.*, 2011[50]	Hip fracture	S (80)	100	(20)	59	3	56	6	9	Yes	Yes	POP	60 d	LeukoR	22	22
Fan *et al.*, 2014[52]	Elective lower limb joint replacement (hip)	80	100	20	56	44	12	NR	NR	Yes	Yes	IOP + POP	Discharge?	NR	NR	NR

(*Continued*)

Table 2. (Continued)

Study Characteristics		Intervention Characteristics														
		Hemoglobin Threshold (g/l)			Not Exposed to Allogeneic Blood (%)			Nonadherence* (%)		Success					Mean Storage Time (d)	
Study ID	Setting or Reason for Admission	Restrictive	Liberal	Δ	Restrictive	Liberal	Δ	Restrictive	Liberal	Mean Erythrocyte UI Differed Significantly between Groups?	Hemoglobin Levels Differed Significantly over Time?	Protocol Application	Follow-up	Type of Erythrocyte (Leukoreduction, Volume, Mean Hematocrit)	Restrictive	Liberal
Foss *et al.*, 2009[8]	Hip fracture	80	100	20	63	27	36	**NR**	**NR**	Yes	No	POP	30 d?	Non-LeukoR	NR	NR
Gregersen *et al.*, 2015[9]	Hip fracture	97	113	16	25	0	25	6	6	Yes	Yes	POP	90 d	LeukoR, 300ml, erythrocyte > 1.65g/dl	Up to 5 wk	Up to 5 wk
Grover *et al.*, 2006[54]	Elective lower limb joint replacement	80	100	20	66	58	8	NR	NR	Yes	Yes	POP	Discharge	LeukoR	NR	NR
Nielsen *et al.*, 2014[62]	Elective hip revision	73	89	16	**67**	**52**	**15**	**18**	**NR**	No	No	IOP + POP	30 d	NR	NR	NR
Parker, 2013[63]	Hip fracture	S	100	NA	89	**NR**	**NA**	**NR**	**NR**	NR	NR	POP	1 yr	NR	NR	NR
So-Osman *et al.*, 2010[68]	Elective lower limb joint replacement	Standardized schema	Non-standardized	**NA**	**65**	**69**	**–4**	**NA**	**NR**	No	No	IOP + POP	Discharge	LeukoR	NR	NR
Group 3: Mixed medical/surgical cases, acute care																
de Almeida *et al.*, 2015[7]	Surveillance post–major abdominal surgery	70	90	20	79	58	21	7	13	Unclear	Yes	POP (ICU only)	30 d	LeukoR, 250–350ml, hematocrit 70%	10	13
Fortune *et al.*, 1987[53]	Trauma or surgical bleeding	100*	133*	33	**NR**	**NR**	**NA**	**NR**	**NR**	Unclear	Yes	ICU stay	3 d	NR	NR	NR
Hébert *et al.*, 1995[57]	Various diagnoses	70–75	100–105	30	46	3	43	6	6	Yes	Yes	ICU stay	30 d	NR	NR	NR
Hébert *et al.*, 1999[56]	Various diagnoses	70	100	30	33	0	33	1	3	Yes	Yes	ICU stay	60 d	LeukoR, 240–340ml, hematocrit 80%	NR	NR
Holst et al., 2014[58]	Septic shock	70	90	20	36	1	35	9	21	Yes	Yes	ICU stay (max 90 d)	356 d	LeukoR	NR	NR
Jairath *et al.*, 2015[35]	Upper-GI bleeding	80	100	20	**67**	**54**	**13**	2	**24**	No	No	Discharge	28 d	NR	NR	NR

(*Continued*)

Table 2. (Continued)

Study Characteristics		Intervention Characteristics														
		Hemoglobin Threshold (g/l)			Not Exposed to Allogeneic Blood (%)			Nonadherence* (%)		Success					Mean Storage Time (d)	
Study ID	Setting or Reason for Admission	Restrictive	Liberal	Δ	Restrictive	Liberal	Δ	Restrictive	Liberal	Mean Erythrocyte UI Differed Significantly between Groups?	Hemoglobin Levels Differed Significantly over Time?	Protocol Application	Follow-up	Type of Erythrocyte (Leukoreduction, Volume, Mean Hematocrit)	Restrictive	Liberal
Markatou *et al.*, 2012[59]	Surveillance post major abdominal surgery	77	99	22	64	30	34	NR	NR	Yes	Yes	IOP + POP	Discharge	NR	22	28
Topley and Fisher 1956[69]	Trauma	70–80% of RCV	Normal RCV	NA	33	0	33	80		Yes	Yes	NR	NR	NR	NR	NR
Villanueva *et al.*, 2013[70]	Upper-GI bleeding	70	90	20	51	41	10	9	3	Yes	Yes	Until discharge	45 d	LeukoR, 250–320 ml, hematocrit 60%	15	15
Walsh *et al.*, 2013[36]	Various diagnoses	70	90	20	22	0	22	14	37	Yes	Yes	ICU stay (maximum 14 d)	180 d	LeukoR, 220-340 ml, hematocrit 50–70%†	21	21
Group 4: Younger, fitter, brain injury/intracranial bleeding																
Naidech *et al.*, 2010[61]	Neuro-ICU	100	115	15	19	5	14	0	10	Yes	Yes	14 d	3 mo	Leukodepleted	24	26
Robertson *et al.*, 2014[65]	Neuro-ICU	70	100	30	48	28	20	4	0	Yes	Yes	End of ventilation/ ICP monitoring	6 mo	Leukodepleted	NR	NR
Group 5: Other patients and settings																
Prick *et al.*, 2014[64]	Postpartum hemorrhage	S	89	NA	87	3	84	1	3	Yes	Yes	Discharge	6 wk	NR	NR	NR
Webert *et al.*, 2008[71]	Hematologic cancer	80	120	40	**10**	**7**	**3**	**36**	**NR**	Unclear	Yes	NR	25 d	Leukodepleted, 240–340 ml, hematocrit 55–65%	NR	NR

Studies with significant differences in mean erythrocyte units/group and in hemoglobin levels over time were deemed successful, *i.e.,* demonstrating successful transfusion protocol implementation. The absolute difference in transfusion thresholds between groups (Δ hemoglobin threshold), the transfusion-sparing effect (Δ exposure to allogeneic blood), and nonadherence rates were considered as determinants for success. Variables in **bold** indicate why transfusion protocol implementation may have failed. Variables in *italic* correspond to hematocrit values converted to hemoglobin values.

*Nonadherence was defined as any violation resulting in a dilution of the protocol effect (such as situations where patients in the restrictive group were transfused above the prescribed threshold or situations where patients in the liberal group where not transfused, although this would have been indicated. †Reported as "standard U.K. blood" in the original article; interpretation based on: Handbook of transfusion medicine, United Kingdom Blood Services, 5th edition, 2013. Available at: http://www.transfusionguidelines.org.uk/transfusion-handbook.

CABG = coronary artery bypass graft; CV = cardiovascular; GI = gastrointestinal; ICP = intracranial pressure measurement; ICU = intensive care unit; IOP = intraoperative; LeukoR = leukoreduced; NA = not applicable; NR = not reported; POP = postoperative; RCV = red cell volume; S = symptoms of anemia; UI = units.

Supplemental Digital Content 11, http://links.lww.com/ALN/B285, which outlines outcome reporting across studies). Outcomes could not be extracted in one study reporting "neuropsychiatric complications."[68] Thus, data from 7 studies (3,465 patients) were combined[8,49,50,52,54,63,68]: in an elderly population undergoing orthopedic surgery, events reflecting inadequate oxygen supply were significantly increased in the restrictive group (RR, 1.41; 95% CI, 1.03 to 1.92).

In group 3, six studies reported "inadequate oxygen" events (see table, Supplemental Digital Content 11, http://links.lww.com/ALN/B285, which outlines outcome reporting across studies).[7,56,58,70] Data from one study could not be extracted, since events were reported as composite outcomes.[56] When data were combined, there was no difference between groups (3,590 patients; RR, 0.89; 95% CI, 0.72 to 1.09).

Among group 4 and 5 studies, only one study reported the incidence of stroke.[61] In this trial, patients with subarachnoid hemorrhage at risk of cerebral vasospasm were allocated to high transfusion thresholds. There was no difference between groups (RR, 1.36; 95% CI, 0.59 to 3.15).

Early Mortality. (See fig., Supplemental Digital Content 12, http://links.lww.com/ALN/B286, which illustrates the risk of early mortality.) Most group 1 to 3 studies reported early mortality (see table, Supplemental Digital Content 11, http://links.lww.com/ALN/B285, which outlines outcome reporting across studies). When data were combined, there was a possible increase in events when a restrictive strategy was applied in group 1 (RR, 1.39; 95% CI, 0.95 to 2.04—7 studies, 3,245 patients)[6,47,48,51,55,60,66] but not in group 2 (RR, 1.09; 95% CI, 0.80 to 1.49—7 studies, 3,546 patients)[8,9,49,50,54,63,68] or group 3 (RR, 0.94; 95% CI, 0.73 to 1.20—7 studies, 2,894 patients).[7,35,36,56–59] Mortality was not reported in groups 4 and 5.

Composite Events "Inadequate Oxygen Supply + Mortality" (fig. 2)

The risk of events was significantly increased when patients were assigned to a restrictive transfusion strategy in group 1 (RR, 1.12; 95% CI, 1.01 to 1.24—8 studies, 3,322 patients)[6,47,48,51,55,60,66,67] and group 2 (RR, 1.24; 95% CI, 1.00 to 1.54—8 studies, 3,749 patients)[8,9,49,50,52,54,63,68] but not in group 3 (RR, 0.90; 95% CI, 0.74 to 1.10—8 studies, 3,762 patients).[7,35,36,56–59,70] Data in groups 4 and 5 were too scarce to allow statistical combination.

Immunomodulatory Effects of Allogeneic Blood Transfusions (fig. 3)

The incidence of infections was reported in the majority of included studies (see table, Supplemental Digital Content 11, http://links.lww.com/ALN/B285, which outlines outcome reporting across studies). In groups 1 and 3, no difference was found (group 1: RR, 1.11; 95% CI, 0.94 to 1.31—6 studies, 3,141 patients[6,47,55,60,66,67]; group 3: RR, 0.99; 95% CI, 0.85 to 1.17—5 studies, 2,616 patients[7,35,56,59,70]). In group 2, patients assigned to a restrictive policy seemed to have less septic events (RR, 0.75; 95% CI, 0.53 to 1.04—9 studies, 3,815 patients).[8,9,49,50,52,54,62,63,68] In group 4, both studies reported the incidence of infection, but transfusion protocols were deemed too heterogeneous for statistical combination. When individually assessed, no difference was found (RR, 0.77; 95% CI, 0.51 to 1.16[65]; RR, 0.91; 95% CI, 0.14 to 5.92[61]). Finally, in a study conducted in the postpartum setting, there was no difference between groups (RR, 1.08; 95% CI, 0.63 to 1.87).[64]

We found significant interaction between risk strata, thereby indicating that our context-specific approach was appropriate (inadequate oxygen supply: Cochran Q $P = 0.003$, $I^2 = 82.7\%$; early mortality: $P = 0.11$ but $I^2 = 54.2\%$; composite outcome: $P = 0.0007$, $I^2 = 86.1\%$; infections: $P = 0.04$, $I^2 = 69.1\%$). Data pooling without controlling for clinical heterogeneity (*i.e.*, no context-specific approach) resulted in a dilution of the intervention effect (inadequate oxygen supply: RR, 1.02; 95% CI, 0.94 to 1.11; early mortality: RR, 1.00; 95% CI, 0.89 to 1.12; composite outcome: RR, 1.01; 95% CI, 0.95 to 1.08; infections: RR, 1.97; 95% CI, 0.89 to 1.07).

Additional Analyses

The effect of successful protocol implementation on the risk of AE was explored by excluding unsuccessful studies from each analysis (see table, Supplemental Digital Content 13, http://links.lww.com/ALN/B287, which outlines how risk estimates varied according to successful protocol implementation). In group 1, risk estimates increased further away from the null: patients in the restrictive group seemed to have more events reflecting inadequate oxygen supply (RR, 1.12; 95% CI, 0.99 to 1.27), a 59% increase in mortality (RR, 1.59; 95% CI, 1.04 to 2.44) and a significant increase in the composite outcome (RR, 1.16; 95% CI, 1.03 to 1.31). However, these findings were not reproducible for groups 2 and 3: risk estimates decreased toward the null or further in favor of a restrictive strategy. The effect of successful implementation on infections was inconsistent.

We also explored the effect of cointerventions on the risk of AE, but data were scarce and comparison across studies was difficult (see table, Supplemental Digital Content 14, http://links.lww.com/ALN/B288, which illustrates cointerventions across studies). The use of clotting factor concentrates or antifibrinolytics was reported in three cardiac and one orthopedic surgery studies.[55,60,62,66] Their administration was well balanced between transfusion groups. The use of cryoprecipitate, fresh frozen plasma, and platelets was reported in four,[35,55,60,66] eight,[35,52,55,58,60,62,66,70] and seven studies,[35,55,58,60,66,70,71] respectively. Overall, the administration of blood products was similar between transfusion groups (cryoprecipitate: RR, 0.99; 95% CI, 0.77 to 1.27; fresh frozen plasma: RR, 0.89; 95% CI, 0.75 to 1.04); platelet therapy: RR, 0.95; 95% CI, 0.81 to 1.12), but compared to others, patients undergoing cardiac surgery were more

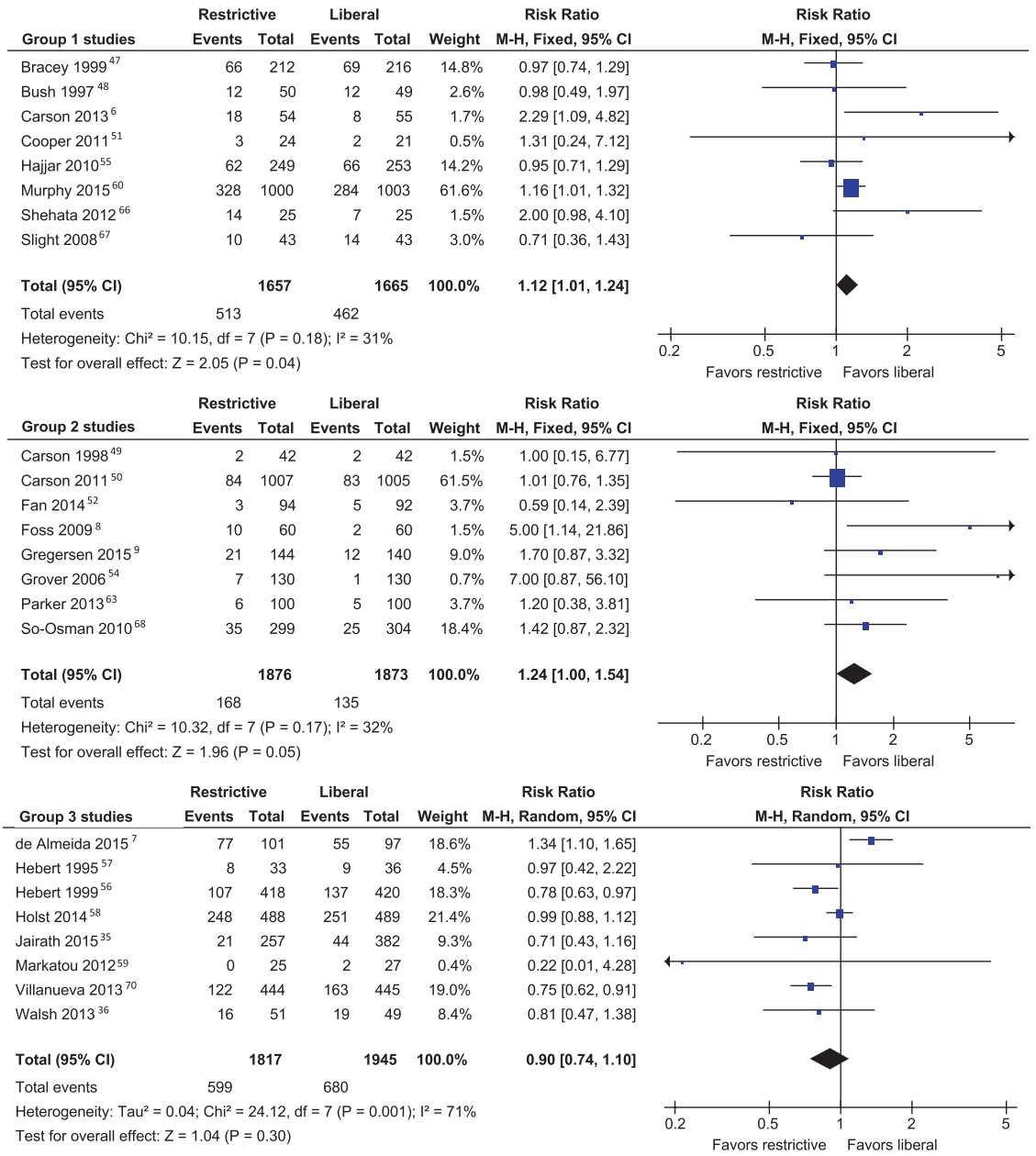

Fig. 2. Forest plots illustrating the risk of composite events. For Jairath *et al*.[35] and Walsh *et al*.,[36] data were obtained by contacting the authors. Composite events: myocardial infarction, arrhythmia, unstable angina, stroke, acute kidney injury, mesenteric ischemia, peripheral ischemia, and mortality (occurring within 30 days); group 1 studies: patients with cardiovascular disease undergoing cardiac or vascular procedures (surgery or catheterization); group 2 studies: elderly patients undergoing orthopedic surgery; group 3 studies: mixed surgical/medical patient population admitted to an acute care facility (emergency or intensive care unit). M-H = Mantel-Haenszel data analysis.

systematically exposed to nonerythrocyte blood products. Finally, 10 studies reported intravenous fluid usage: in only three, unbalanced administration was found.[52,57,62]

Exploring the effect of studies at high or unclear risk of detection and attrition bias did not yield clinically meaningful results: because of the small remaining number of studies, 95% CI was large and risk estimates varied only mildly (data not shown).

Discussion

In this context-specific systematic review, we found that restrictive transfusion strategies were associated with an increased risk of complications in situations combining high-risk patients with major surgery. Those with cardiovascular disease undergoing cardiac or vascular procedures seemed to have more events reflecting inadequate oxygen supply, higher mortality rates, or both. In the elderly orthopedic

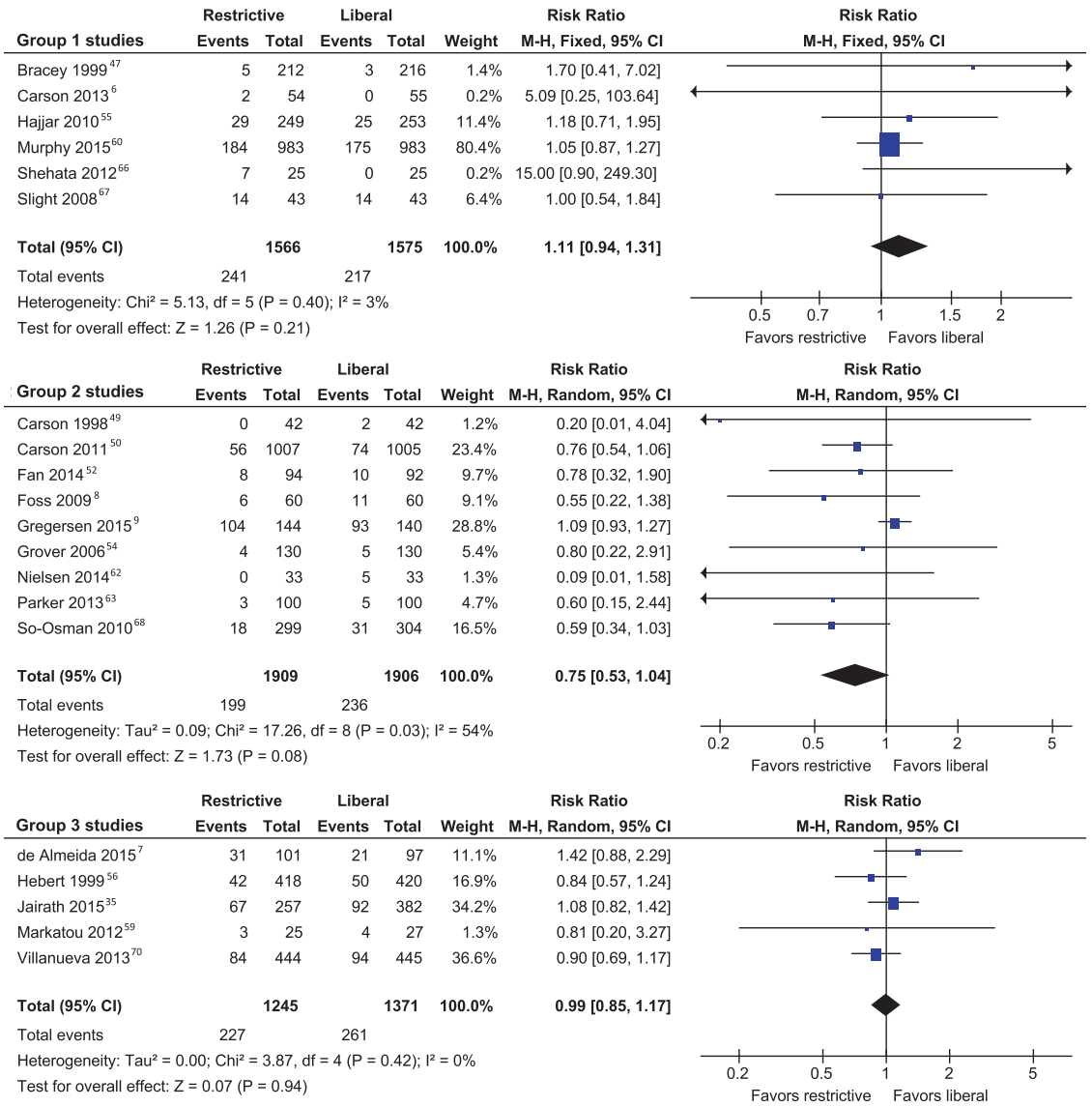

Fig. 3. Forest plots illustrating the risk of infection. Group 1 studies: patients with cardiovascular disease undergoing cardiac or vascular procedures (surgery or catheterization); group 2 studies: elderly patients undergoing orthopedic surgery; group 3 studies: mixed surgical/medical patient population admitted to an acute care facility (emergency or intensive care unit). M-H = Mantel-Haenszel data analysis.

population, a restrictive policy led to a 40% increase in ischemic events or AKI.

These findings were consistent with physiologic studies suggesting that multiple perioperative factors may undermine normal compensatory responses to anemia[72,73]: cardiac dysfunction (induced by anesthetic drugs or surgical trauma), vasoconstriction (due to endogenous or exogenous catecholamines), or postoperative hypoventilation (due to pain or residual effects of anesthetics) may compromise adequate oxygen delivery to vital organs. In normal conditions, systemic oxygen delivery largely exceeds oxygen consumption, resulting in a positive *oxygen reserve*.[73] In patients having a preexisting low reserve, however, the combination of acute anemia with impaired compensatory responses may induce a state of *oxygen supply dependency*, resulting in acidosis and organ failure. In this particular situation, administrating erythrocyte could restore the oxygen reserve by increasing blood oxygen content and tissue oxygenation.[73]

Surprisingly, no evidence of harm was found when restrictive strategies were applied in critically ill patients, although similar impairment of compensatory responses was expected. One explanation might be the heterogeneity in oxygen reserve among this mixed population: medical patients might be at lower risk of oxygen supply dependency than their surgical counterparts, who have the additional burden of surgery, pain, and recovery from anesthesia.

When we excluded studies showing unsuccessful protocol implementation, effect estimates differed across risk strata. While harm was more pronounced in patients undergoing cardiac or vascular procedures, it decreased toward the null in those undergoing orthopedic surgery. Two reasons may account for this: first, cardiac patients were probably more likely to enter a state of oxygen supply dependency (due to the combination of advanced cardiovascular disease and high-risk surgery) than the orthopedic population, where ischemic heart disease ranged from 10 to 45%. Second, cardiac patients might have been exposed to context-specific factors increasing their risk of AE: antifibrinolytics and clotting factor concentrates were more systematically administered in this population, while this was rarely reported in orthopedic patients. Although tranexamic acid seems safe in trauma patients,[74] the thrombogenic potential of other hemostatic agents in nontrauma settings remains unclear.[75–77] Thus, the combination of a restrictive transfusion strategy and highly thrombogenic drugs in patients with advanced cardiovascular disease might be particularly unfavorable.

Our analysis of the risk of infection remained inconclusive. Although there was a possible reduction in septic events in orthopedic patients assigned to a restrictive strategy, effect estimates differed widely across risk strata: the benefit of reduced exposure to allogeneic blood was less clear in cardiac patients, which is consistent with a previously published meta-analysis.[10] One reason might be that immune response impairment was more pronounced in these patients: in our analysis, the cardiac surgery population was more likely to receive nonerythrocyte allogeneic blood products (such as platelets or fresh frozen plasma), which are also known to have immunomodulatory effects.[33,78–80] Alternatively, cardiac surgery itself might induce particularly high levels of perioperative stress, which has also been found to interfere with immune responses.[22,81–83]

Our systematic review differs from others in many aspects. First, in most previous meta-analyses, data were combined despite high clinical heterogeneity,[10,13,14,16] which may hinder the identification of group-specific effects. We addressed this methodologic limitation by performing a *context-specific* analysis, using strict criteria for risk-strata generation and subsequent data pooling. We were eventually able to show that indiscriminate data combination (*i.e.*, performing analyses without controlling for clinical diversity) resulted in a dilution of the intervention effects. Furthermore, to fully explore the impact of clinical diversity, the issue of transfusion protocol variability was examined using two performance indicators and exploring three different determinants of success. One other meta-analysis investigated protocol diversity, but only hemoglobin thresholds were explored.[10] Additionally, our review was the first to assess the role of cointerventions: we were able to show that in some patients, the combination of restrictive transfusion policies and thrombogenic drugs could be particularly detrimental; we also identified a possible effect of nonerythrocyte blood products and of perioperative stressors on the risk of infection.

This review has some limitations. First, although strict criteria were used to handle unclear/missing outcome data, outcome reporting and definitions varied across studies, and so this may result in residual clinical diversity. However, a certain degree of heterogeneity is desirable to ensure wide applicability of the findings. Second, in order to capture the full spectrum of effects related to transfusion strategies and to improve statistical precision, we used arbitrarily defined outcome categories. However, although endpoints combination might be biologically well founded, individual components may differ in clinical importance, and our categories may have failed to reflect endpoints truly relevant for patients.[30] Third, in some risk strata, large studies having high event rates appeared to dominate the analysis, but the risk of a small-study effect was deemed low: we used the Mantel-Haenszel method to account for smaller studies and addressed thoroughly all sources of clinical and methodologic diversity. It seems therefore unlikely that our findings derive solely from the effect of larger studies. Fourth, our assessment of methodologic heterogeneity (detection and attrition bias) was hampered by the scarcity of data. The same problem was encountered with data on cointerventions, which reduced our ability to fully explore their role in the occurrence of complications. Finally, indicators of successful protocol implementation were arbitrarily defined; using a different model might have yielded other results.

This analysis provided clear evidence that the decision to transfuse (or not transfuse) requires more than a "one-size-fits-all" approach. As highlighted recently,[84–86] the identification of populations at higher risk of oxygen supply dependency who might particularly benefit from erythrocyte administration remains a real challenge. New transfusion algorithms should aim to integrate additional clinical parameters, such as patient comorbidities, particular settings, or oxygen reserve estimates.[73] We recommend that future trials systematically collect and report data regarding the use of nonerythrocyte blood products, antifibrinolytics, and clotting factor concentrates, since their role in the risk of AE remains unclear.

Conclusion

This meta-analysis suggests that the use of restrictive transfusion strategies might be detrimental in high-risk patients undergoing major surgery. Further research is needed to evaluate the contributing role of cointerventions in the occurrence of complications.

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Competing Interests

The authors declare no competing interests. The funding organizations had no role in the design and conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Reproducible Science

Full protocol available from Dr. Hovaguimian: frederique.hovaguimian@usz.ch. Raw data available from Dr. Hovaguimian: frederique.hovaguimian@usz.ch.

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References

1. Shaw RE, Johnson CK, Ferrari G, Brizzio ME, Sayles K, Rioux N, Zapolanski A, Grau JB: Blood transfusion in cardiac surgery does increase the risk of 5-year mortality: Results from a contemporary series of 1714 propensity-matched patients. Transfusion 2014; 54:1106–13
2. Turan A, Yang D, Bonilla A, Shiba A, Sessler DI, Saager L, Kurz A: Morbidity and mortality after massive transfusion in patients undergoing non-cardiac surgery. Can J Anaesth 2013; 60:761–70
3. Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, Salloum R, Meredith UW, Osler TM: Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology 2011; 114:283–92
4. Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB: Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg 2009; 208:931–7, 937.e1–2; discussion 938–9
5. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ: The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States. Crit Care Med 2004; 32:39–52
6. Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, Srinivas V, Menegus MA, Marroquin OC, Rao SV, Noveck H, Passano E, Hardison RM, Smitherman T, Vagaonescu T, Wimmer NJ, Williams DO: Liberal *versus* restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013; 165:964–971.e1
7. de Almeida JP, Vincent JL, Galas FR, de Almeida EP, Fukushima JT, Osawa EA, Bergamin F, Park CL, Nakamura RE, Fonseca SM, Cutait G, Alves JI, Bazan M, Vieira S, Sandrini AC, Palomba H, Ribeiro U Jr, Crippa A, Dallogllio M, Diz Mdel P, Kalil Filho R, Auler JO Jr, Rhodes A, Hajjar LA: Transfusion requirements in surgical oncology patients: A prospective, randomized controlled trial. Anesthesiology 2015; 122:29–38
8. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H: The effects of liberal *versus* restrictive transfusion thresholds on ambulation after hip fracture surgery. Transfusion 2009; 49:227–34
9. Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture. Acta Orthopaedica 2015:1–10
10. Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L, Hickner A, Rogers MA: Health care-associated infection after red blood cell transfusion: A systematic review and meta-analysis. JAMA 2014; 311:1317–26
11. Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, Stanworth S: Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev 2015; 4:CD009699
12. Deeks J, Higgins J, Altman D. Chapter 9: Analysing data and undertaking meta-analyses, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Edited by Higgins JPT, Green S. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. Accessed March 30, 2016
13. Carson JL, Carless PA, Hebert PC: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2012; 4:CD002042
14. Curley GF, Shehata N, Mazer CD, Hare GM, Friedrich JO: Transfusion triggers for guiding RBC transfusion for cardiovascular surgery: A systematic review and meta-analysis*. Crit Care Med 2014; 42:2611–24
15. Jairath V, Hearnshaw S, Brunskill SJ, Doree C, Hopewell S, Hyde C, Travis S, Murphy MF. Red cell transfusion for the management of upper gastrointestinal haemorrhage. Cochrane Database Syst Rev 2010:CD006613
16. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J: Restrictive *versus* liberal transfusion strategy for red blood cell transfusion: Systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ 2015; 350:h1354
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 2009; 339:b2535
18. von Elm E, Poglia G, Walder B, Tramèr MR: Different patterns of duplicate publication: An analysis of articles used in systematic reviews. JAMA 2004; 291:974–80
19. Higgins J, Deeks J, Altman D. Chapter 16: Special topics in statistics, Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (Updated March 2011). Edited by Higgins JPT, Green S. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. Accessed March 30, 2016
20. Vanderlinde ES, Heal JM, Blumberg N: Autologous transfusion. BMJ 2002; 324:772–5
21. Carless P, Moxey A, O'Connell D, Henry D: Autologous transfusion techniques: A systematic review of their efficacy. Transfus Med 2004; 14:123–44
22. Kim TH, Koh YS, Chang K, Seo SM, Kim CJ, Park HJ, Kim PJ, Her SH, Kim DB, Lee JM, Park CS, Kim HY, Yoo KD, Jeon DS, Park JH, Chung WS, Seung KB; CathOlic university of Korea—percutAneous Coronary inTervention Registry Investigators: Improved anemia is associated with favorable long-term clinical outcomes in patients undergoing PCI. Coron Artery Dis 2012; 23:391–9
23. Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G, Sharma SC, Vezeridis M, Khuri SF, Friedmann PD: Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007; 297:2481–8
24. Sakr Y, Lobo S, Knuepfer S, Esser E, Bauer M, Settmacher U, Barz D, Reinhart K: Anemia and blood transfusion in a surgical intensive care unit. Crit Care 2010; 14:R92
25. Saager L, Turan A, Reynolds LF, Dalton JE, Mascha EJ, Kurz A: The association between preoperative anemia and 30-day

mortality and morbidity in noncardiac surgical patients. Anesth Analg 2013; 117:909–15

26. Sekhon MS, McLean N, Henderson WR, Chittock DR, Griesdale DE: Association of hemoglobin concentration and mortality in critically ill patients with severe traumatic brain injury. Crit Care 2012; 16:R128
27. Shema-Didi L, Ore L, Geron R, Kristal B: Is anemia at hospital admission associated with in-hospital acute kidney injury occurrence? Nephron Clin Pract 2010; 115:c168–76
28. De Santo L, Romano G, Della Corte A, de Simone V, Grimaldi F, Cotrufo M, de Feo M: Preoperative anemia in patients undergoing coronary artery bypass grafting predicts acute kidney injury. J Thorac Cardiovasc Surg 2009; 138:965–70
29. Montori VM, Permanyer-Miralda G, Ferreira-González I, Busse JW, Pacheco-Huergo V, Bryant D, Alonso J, Akl EA, Domingo-Salvany A, Mills E, Wu P, Schünemann HJ, Jaeschke R, Guyatt GH: Validity of composite end points in clinical trials. BMJ 2005; 330:594–6
30. Myles PS, Devereaux PJ: Pros and cons of composite endpoints in anesthesia trials. Anesthesiology 2010; 113:776–8
31. Wallis JP, Wells AW, Whitehead S, Brewster N: Recovery from post-operative anaemia. Transfus Med 2005; 15:413–8
32. Bateman AP, McArdle F, Walsh TS: Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. Crit Care Med 2009; 37:1906–12
33. Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI: Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. Br J Anaesth 2013; 110:690–701
34. Refaai MA, Blumberg N: Transfusion immunomodulation from a clinical perspective: An update. Expert Rev Hematol 2013; 6:653–63
35. Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, James MW, Stanley AJ, Everett SM, Bailey AA, Dallal H, Greenaway J, Le Jeune I, Darwent M, Church N, Reckless I, Hodge R, Dyer C, Meredith S, Llewelyn C, Palmer KR, Logan RF, Travis SP, Walsh TS, Murphy MF: Restrictive *versus* liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): A pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015; 386:137–44
36. Walsh TS, Boyd JA, Watson D, Hope D, Lewis S, Krishan A, Forbes JF, Ramsay P, Pearse R, Wallis C, Cairns C, Cole S, Wyncoll D; RELIEVE Investigators: Restrictive *versus* liberal transfusion strategies for older mechanically ventilated critically ill patients: A randomized pilot trial. Crit Care Med 2013; 41:2354–63
37. Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). Edited by Higgins JPT, Green S. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. Accessed March 30, 2016
38. Loke Y, Price D, A H. Chapter 14: Adverse effects, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). Edited by Higgins JPT, Green S. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. Accessed March 30, 2016
39. Sedgwick P. Meta-analyses: Heterogeneity and subgroup analysis. BMJ 2013; 346:f4040
40. Groenwold RH, Rovers MM, Lubsen J, van der Heijden GJ: Subgroup effects despite homogeneous heterogeneity test results. BMC Med Res Methodol 2010; 10:43
41. Gregersen M, Damsgaard EM, Borris LC: Blood transfusion and risk of infection in frail elderly after hip fracture surgery: The TRIFE randomized controlled trial. Eur J Orthop Surg Traumatol 2015; 25:1031–8
42. Gregersen M, Borris LC, Damsgaard EM: Blood transfusion and overall quality of life after hip fracture in frail elderly patients—The transfusion requirements in frail elderly randomized controlled trial. J Am Med Dir Assoc 2015; 16:762–6
43. Slight RD, Fung AK, Alonzi C, Bappu NJ, McClelland DB, Mankad PS: Rationalizing blood transfusion in cardiac surgery: Preliminary findings with a red cell volume-based model. Vox Sang 2007; 92:154–6
44. Gruber-Baldini AL, Marcantonio E, Orwig D, Magaziner J, Terrin M, Barr E, Brown JP, Paris B, Zagorin A, Roffey DM, Zakriya K, Blute MR, Hebel JR, Carson JL: Delirium outcomes in a randomized trial of blood transfusion thresholds in hospitalized older adults with hip fracture. J Am Geriatr Soc 2013; 61:1286–95
45. Carson JL, Sieber F, Cook DR, Hoover DR, Noveck H, Chaitman BR, Fleisher L, Beaupre L, Macaulay W, Rhoads GG, Paris B, Zagorin A, Sanders DW, Zakriya KJ, Magaziner J: Liberal *versus* restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. Lancet 2015; 385:1183–9
46. Jiwaji Z, Nunn KP, Conway-Morris A, Simpson AJ, Wyncoll D, Rossi AG, Walsh TS; RELIEVE Trial Investigators: Leukoreduced blood transfusion does not increase circulating soluble markers of inflammation: A randomized controlled trial. Transfusion 2014; 54:2404–11
47. Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, Radovancevic B, McAllister HA Jr, Cooley DA: Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: Effect on patient outcome. Transfusion 1999; 39:1070–7
48. Bush RL, Pevec WC, Holcroft JW: A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. Am J Surg 1997; 174:143–8
49. Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, Magaziner J, Merlino FE, Bunce G, McClelland B, Duff A, Noveck H: A pilot randomized trial comparing symptomatic *vs.* hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion 1998; 38:522–9
50. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J; FOCUS Investigators: Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453–62
51. Cooper HA, Rao SV, Greenberg MD, Rumsey MP, McKenzie M, Alcorn KW, Panza JA: Conservative *versus* liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol 2011; 108:1108–11
52. Fan YX, Liu FF, Jia M, Yang JJ, Shen JC, Zhu GM, Zhu SH, Li WY, Yang JJ, Ji MH: Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: A preliminary study. Arch Gerontol Geriatr 2014; 59:181–5
53. Fortune JB, Feustel PJ, Saifi J, Stratton HH, Newell JC, Shah DM: Influence of hematocrit on cardiopulmonary function after acute hemorrhage. J Trauma 1987; 27:243–9
54. Grover M, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, Brett S, Goldhill DR, Soni N: Silent myocardial ischaemia and haemoglobin concentration: A randomized controlled trial of transfusion strategy in lower limb arthroplasty. Vox Sang 2006; 90:105–12
55. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, Fukushima J, Kalil Filho R, Sierra DB, Lopes NH, Mauad T, Roquim AC, Sundin MR, Leão WC, Almeida JP, Pomerantzeff PM, Dallan LO, Jatene FB, Stolf NA, Auler JO Jr: Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. JAMA 2010; 304:1559–67
56. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicenter, randomized, controlled clinical trial of transfusion

requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340:409–17

57. Hébert PC, Wells G, Marshall J, Martin C, Tweeddale M, Pagliarello G, Blajchman M: Transfusion requirements in critical care. A pilot study. Canadian Critical Care Trials Group. JAMA 1995; 273:1439–44
58. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, Nebrich L, Nibro HL, Rasmussen BS, Lauridsen JR, Nielsen JS, Oldner A, Pettilä V, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Møller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, Sjøbø B, Bundgaard H, Thyø MA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower *versus* higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014; 371:1381–91
59. Markatou M, Theodoraki K, Rizos D, Fassoulaki A: Targeting perioperative haemoglobin in major abdominal surgery. J Anesth Clin Res 2012; 3:1–6
60. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC; TITRe2 Investigators: Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015; 372:997–1008
61. Naidech AM, Shaibani A, Garg RK, Duran IM, Liebling SM, Bassin SL, Bendok BR, Bernstein RA, Batjer HH, Alberts MJ: Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. Neurocrit Care 2010; 13:313–20
62. Nielsen K, Johansson PI, Dahl B, Wagner M, Frausing B, Børglum J, Jensen K, Stürup J, Hvolris J, Rasmussen LS: Perioperative transfusion threshold and ambulation after hip revision surgery—A randomized trial. BMC Anesthesiol 2014; 14:89
63. Parker MJ: Randomised trial of blood transfusion *versus* a restrictive transfusion policy after hip fracture surgery. Injury 2013; 44:1916–8
64. Prick BW, Jansen AJ, Steegers EA, Hop WC, Essink-Bot ML, Uyl-de Groot CA, Akerboom BM, van Alphen M, Bloemenkamp KW, Boers KE, Bremer HA, Kwee A, van Loon AJ, Metz GC, Papatsonis DN, van der Post JA, Porath MM, Rijnders RJ, Roumen FJ, Scheepers HC, Schippers DH, Schuitemaker NW, Stigter RH, Woiski MD, Mol BW, van Rhenen DJ, Duvekot JJ: Transfusion policy after severe postpartum haemorrhage: A randomised non-inferiority trial. BJOG 2014; 121:1005–14
65. Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC, Baldwin A, Rivera Lara L, Saucedo-Crespo H, Ahmed O, Sadasivan S, Ponce L, Cruz-Navarro J, Shahin H, Aisiku IP, Doshi P, Valadka A, Neipert L, Waguspack JM, Rubin ML, Benoit JS, Swank P; Epo Severe TBI Trial Investigators: Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: A randomized clinical trial. JAMA 2014; 312:36–47
66. Shehata N, Burns LA, Nathan H, Hebert P, Hare GM, Fergusson D, Mazer CD: A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion 2012; 52:91–9
67. Slight RD, O'Donohoe P, Fung AK, Alonzi C, McClelland DB, Mankad PS: Rationalizing blood transfusion in cardiac surgery: The impact of a red cell volume-based guideline on blood usage and clinical outcome. Vox Sang 2008; 95:205–10
68. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A: A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. Vox Sang 2010; 98:56–64
69. Topley E, Fisher MR. The illness of trauma. Br J Clin Pract 1956; 10: 770–6
70. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C: Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013; 368:11–21
71. Webert KE, Cook RJ, Couban S, Carruthers J, Lee KA, Blajchman MA, Lipton JH, Brandwein JM, Heddle NM: A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. Transfusion 2008; 48:81–91
72. Freudenberger RS, Carson JL: Is there an optimal hemoglobin value in the cardiac intensive care unit? Curr Opin Crit Care 2003; 9:356–61
73. Spinelli E, Bartlett RH: Anemia and transfusion in critical care: Physiology and management. J Intensive Care Med 2015:1–12
74. Roberts I, Shakur H, Ker K, Coats T; CRASH-2 Trial Collaborators: Antifibrinolytic drugs for acute traumatic injury. Cochrane Database Syst Rev 2012; 12:CD004896
75. Sørensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R: Clinical review: Prothrombin complex concentrates—Evaluation of safety and thrombogenicity. Crit Care 2011; 15:201
76. Ortmann E, Besser MW, Klein AA: Antifibrinolytic agents in current anaesthetic practice. Br J Anaesth 2013; 111:549–63
77. Tanaka KA, Esper S, Bolliger D: Perioperative factor concentrate therapy. Br J Anaesth 2013; 111(suppl 1):i35–49
78. Juffermans NP, Prins DJ, Vlaar AP, Nieuwland R, Binnekade JM: Transfusion-related risk of secondary bacterial infections in sepsis patients: A retrospective cohort study. Shock 2011; 35:355–9
79. Subramanian A, Berbari EF, Brown MJ, Allen MS, Alsara A, Kor DJ: Plasma transfusion is associated with postoperative infectious complications following esophageal resection surgery: A retrospective cohort study. J Cardiothorac Vasc Anesth 2012; 26:569–74
80. Görlinger K, Saner FH: Prophylactic plasma and platelet transfusion in the critically Ill patient: Just useless and expensive or even harmful? BMC Anesthesiol 2015; 15:86
81. Williams ML, He X, Rankin JS, Slaughter MS, Gammie JS: Preoperative hematocrit is a powerful predictor of adverse outcomes in coronary artery bypass graft surgery: A report from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg 2013; 96:1628–34; discussion 1634
82. Weber WP, Zwahlen M, Reck S, Misteli H, Rosenthal R, Buser AS, Kaufmann M, Oertli D, Widmer AF, Marti WR: The association of preoperative anemia and perioperative allogeneic blood transfusion with the risk of surgical site infection. Transfusion 2009; 49:1964–70
83. Hogan BV, Peter MB, Shenoy HG, Horgan K, Hughes TA: Surgery induced immunosuppression. Surgeon 2011; 9:38–43
84. Roubinian NH, Carson JL: Restrictive red blood cell transfusion strategies appear safe in most clinical settings. Evid Based Med 2015; 20:170
85. Klein HG, Flegel WA, Natanson C: Red blood cell transfusion: Precision *vs* imprecision medicine. JAMA 2015:1–2
86. Docherty AB, O'Donnell R, Brunskill S, Trivella M, Doree C, Holst L, Parker M, Gregersen M, Pinheiro de Almeida J, Walsh TS, Stanworth SJ: Effect of restrictive *versus* liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: Systematic review and meta-analysis. BMJ 2016; 352:i1351