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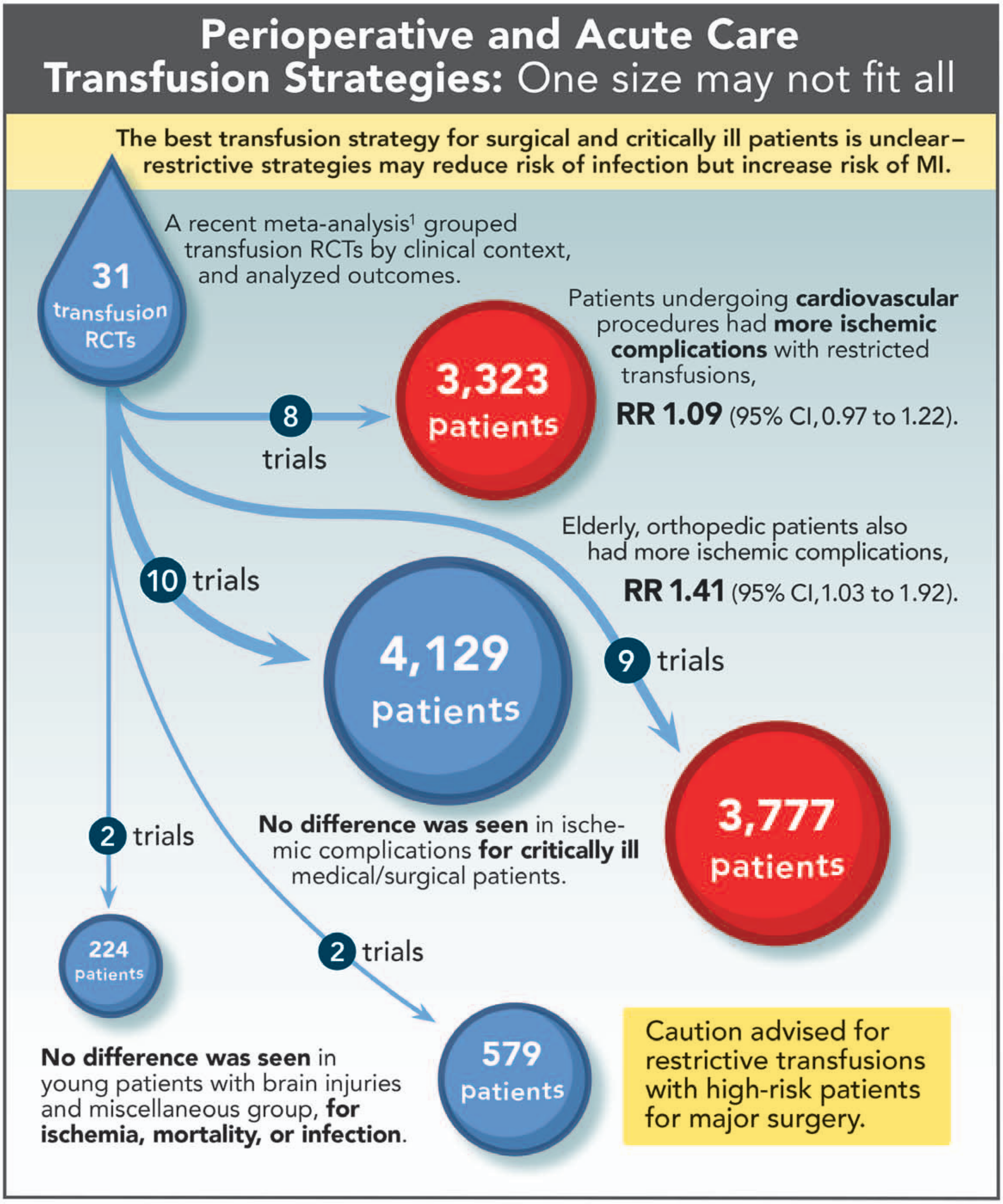

MI = myocardial injury; RCT = randomized, controlled trial; RR = relative risk.

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.

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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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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

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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

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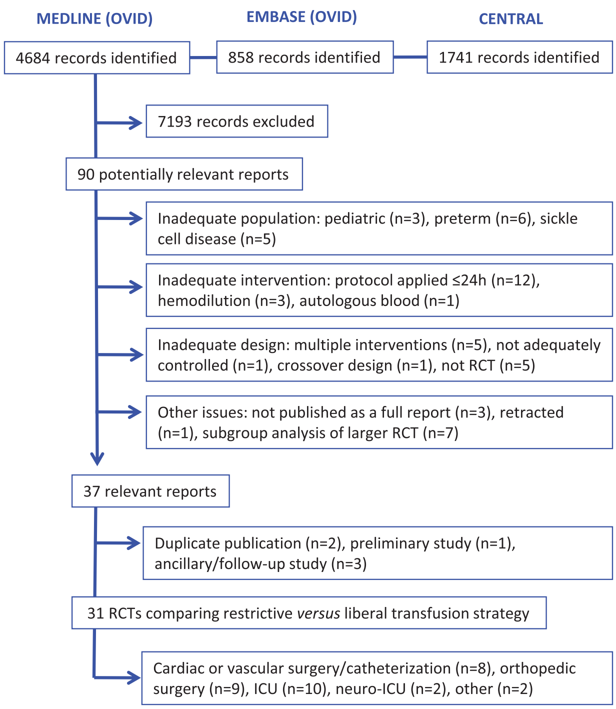

Fig. 1. Flow diagram illustrating the study selection process. ICU = intensive care unit; RCT = randomized controlled trial.

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,

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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 Oral AC Other anti-PLT	151 (71) 4 (2) 11 (5)	147 (68) 4 (2) 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 Other anti-PLT Chronic AC	48 (87) 44 (80) 0	51 (93) 45 (82) 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 Other anti-PLT Heparin Gp antagonist	24 (100) 21 (88) 10 (41) 2 (8)	21 (100) 17 (81) 7 (33) 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 Other anti-PLT	277 (28) 41 (4.1)	284 (28) 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 Oral AC	18 (72) 7 (28)	17 (68) 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 Chronic AC	12 (28.6) 14 (33.3)	15 (35.7) 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*)

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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.

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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 catheterization 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*)

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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 > 1.65 g/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, 250–350 ml, 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, 240–340 ml, 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*)

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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.

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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

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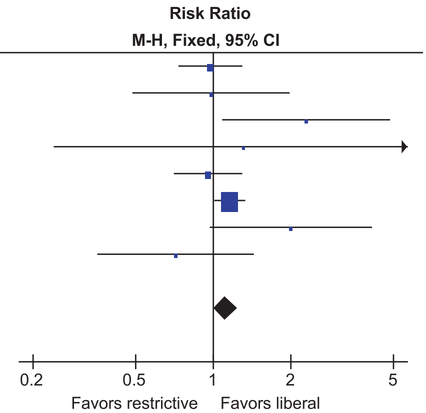
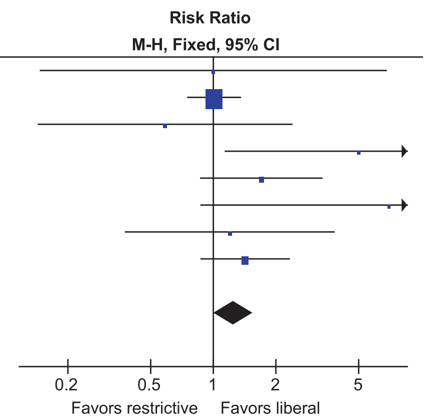
Group 1 studies	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bracey 1999 [47]	66	212	69	216	14.8%	0.97 [0.74, 1.29]
Bush 1997 [48]	12	50	12	49	2.6%	0.98 [0.49, 1.97]
Carson 2013 [6]	18	54	8	55	1.7%	2.29 [1.09, 4.82]
Cooper 2011 [51]	3	24	2	21	0.5%	1.31 [0.24, 7.12]
Hajjar 2010 [55]	62	249	66	253	14.2%	0.95 [0.71, 1.29]
Murphy 2015 [60]	328	1000	284	1003	61.6%	1.16 [1.01, 1.32]
Shehata 2012 [66]	14	25	7	25	1.5%	2.00 [0.98, 4.10]
Slight 2008 [67]	10	43	14	43	3.0%	0.71 [0.36, 1.43]
Total (95% CI)		**1657**		**1665**	**100.0%**	**1.12 [1.01, 1.24]**
Total events	513		462			

Heterogeneity: Chi² = 10.15, df = 7 (P = 0.18); I² = 31%
Test for overall effect: Z = 2.05 (P = 0.04)



Group 2 studies	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carson 1998 [49]	2	42	2	42	1.5%	1.00 [0.15, 6.77]
Carson 2011 [50]	84	1007	83	1005	61.5%	1.01 [0.76, 1.35]
Fan 2014 [52]	3	94	5	92	3.7%	0.59 [0.14, 2.39]
Foss 2009 [8]	10	60	2	60	1.5%	5.00 [1.14, 21.86]
Gregersen 2015 [9]	21	144	12	140	9.0%	1.70 [0.87, 3.32]
Grover 2006 [54]	7	130	1	130	0.7%	7.00 [0.87, 56.10]
Parker 2013 [63]	6	100	5	100	3.7%	1.20 [0.38, 3.81]
So-Osman 2010 [68]	35	299	25	304	18.4%	1.42 [0.87, 2.32]
Total (95% CI)		**1876**		**1873**	**100.0%**	**1.24 [1.00, 1.54]**
Total events	168		135			

Heterogeneity: Chi² = 10.32, df = 7 (P = 0.17); I² = 32%
Test for overall effect: Z = 1.96 (P = 0.05)



Group 3 studies	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
de Almeida 2015 [7]	77	101	55	97	18.6%	1.34 [1.10, 1.65]
Hebert 1995 [57]	8	33	9	36	4.5%	0.97 [0.42, 2.22]
Hebert 1999 [56]	107	418	137	420	18.3%	0.78 [0.63, 0.97]
Holst 2014 [58]	248	488	251	489	21.4%	0.99 [0.88, 1.12]
Jairath 2015 [35]	21	257	44	382	9.3%	0.71 [0.43, 1.16]
Markatou 2012 [59]	0	25	2	27	0.4%	0.22 [0.01, 4.28]
Villanueva 2013 [70]	122	444	163	445	19.0%	0.75 [0.62, 0.91]
Walsh 2013 [36]	16	51	19	49	8.4%	0.81 [0.47, 1.38]
Total (95% CI)		**1817**		**1945**	**100.0%**	**0.90 [0.74, 1.10]**
Total events	599		680			

Heterogeneity: Tau² = 0.04; Chi² = 24.12, df = 7 (P = 0.001); I² = 71%
Test for overall effect: Z = 1.04 (P = 0.30)

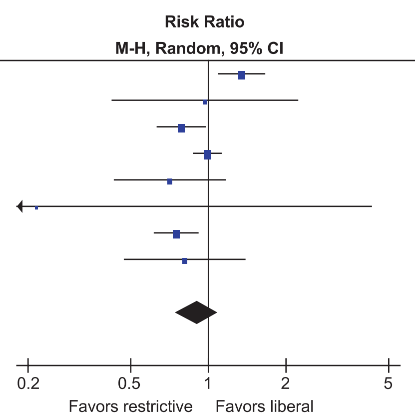


Fig. 2. Forest plots illustrating the risk of composite events. For Jairath *et al.*[35] and Walsh *et al.*,[36] data were obtained by contacting the authors. Composite events: myocardial infarction, arrhythmia, unstable angina, stroke, acute kidney injury, mesenteric ischemia, peripheral ischemia, and 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

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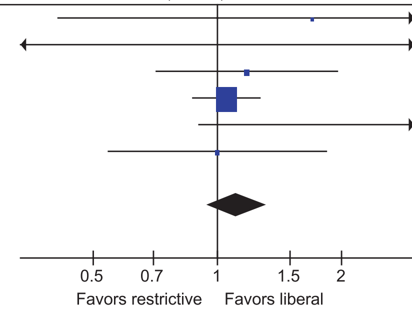
Group 1 studies	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bracey 1999[47]	5	212	3	216	1.4%	1.70 [0.41, 7.02]
Carson 2013[6]	2	54	0	55	0.2%	5.09 [0.25, 103.64]
Hajjar 2010[55]	29	249	25	253	11.4%	1.18 [0.71, 1.95]
Murphy 2015[60]	184	983	175	983	80.4%	1.05 [0.87, 1.27]
Shehata 2012[66]	7	25	0	25	0.2%	15.00 [0.90, 249.30]
Slight 2008[67]	14	43	14	43	6.4%	1.00 [0.54, 1.84]
Total (95% CI)		**1566**		**1575**	**100.0%**	**1.11 [0.94, 1.31]**
Total events	241		217			

Heterogeneity: Chi² = 5.13, df = 5 (P = 0.40); I² = 3%
Test for overall effect: Z = 1.26 (P = 0.21)

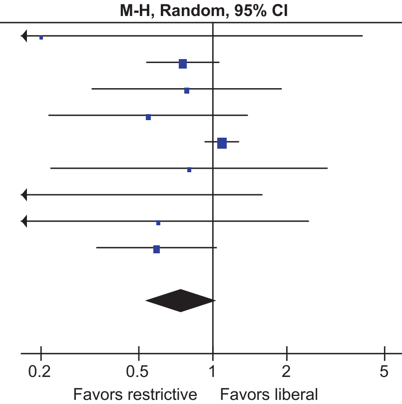
Risk Ratio M-H, Fixed, 95% CI



Group 2 studies	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 1998[49]	0	42	2	42	1.2%	0.20 [0.01, 4.04]
Carson 2011[50]	56	1007	74	1005	23.4%	0.76 [0.54, 1.06]
Fan 2014[52]	8	94	10	92	9.7%	0.78 [0.32, 1.90]
Foss 2009[8]	6	60	11	60	9.1%	0.55 [0.22, 1.38]
Gregersen 2015[9]	104	144	93	140	28.8%	1.09 [0.93, 1.27]
Grover 2006[54]	4	130	5	130	5.4%	0.80 [0.22, 2.91]
Nielsen 2014[62]	0	33	5	33	1.3%	0.09 [0.01, 1.58]
Parker 2013[63]	3	100	5	100	4.7%	0.60 [0.15, 2.44]
So-Osman 2010[68]	18	299	31	304	16.5%	0.59 [0.34, 1.03]
Total (95% CI)		**1909**		**1906**	**100.0%**	**0.75 [0.53, 1.04]**
Total events	199		236			

Heterogeneity: Tau² = 0.09; Chi² = 17.26, df = 8 (P = 0.03); I² = 54%
Test for overall effect: Z = 1.73 (P = 0.08)

Risk Ratio M-H, Random, 95% CI



Group 3 studies	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
de Almeida 2015[7]	31	101	21	97	11.1%	1.42 [0.88, 2.29]
Hebert 1999[56]	42	418	50	420	16.9%	0.84 [0.57, 1.24]
Jairath 2015[35]	67	257	92	382	34.2%	1.08 [0.82, 1.42]
Markatou 2012[59]	3	25	4	27	1.3%	0.81 [0.20, 3.27]
Villanueva 2013[70]	84	444	94	445	36.6%	0.90 [0.69, 1.17]
Total (95% CI)		**1245**		**1371**	**100.0%**	**0.99 [0.85, 1.17]**
Total events	227		261			

Heterogeneity: Tau² = 0.00; Chi² = 3.87, df = 4 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)

Risk Ratio M-H, Random, 95% CI

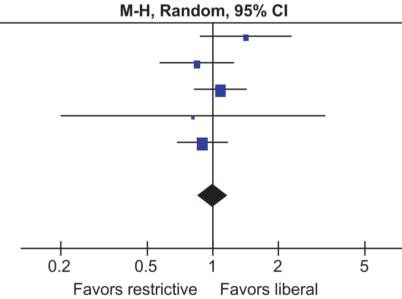


Fig. 3. Forest plots illustrating the risk of infection. Group 1 studies: patients with cardiovascular disease undergoing cardiac or vascular procedures (surgery or catheterization); group 2 studies: elderly patients undergoing orthopedic surgery; group 3 studies: mixed surgical/medical patient population 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.

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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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