REVIEW ARTICLE/BRIEF REVIEW

When to transfuse your acute care patient? A narrative review of the risk of anemia and red blood cell transfusion based on clinical trial outcomes

Quand transfuser un patient en soins aigus? Un compte rendu narratif du risque de l'anémie et de la transfusion d'érythrocytes selon les résultats des études cliniques

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Abstract *This narrative review critically evaluates the evidence for risk of anemia and red blood cell (RBC) transfusion. For this purpose, it assesses large prospective randomized-controlled trials (RCTs) in medical, surgical, and critical care patient populations in which the impact of specific hemoglobin transfusion thresholds are compared. In these trials, the risks of anemia relative to those of RBC transfusion are assessed. The results of published systematic reviews and meta-analyses are also discussed.*

Lastly, recommendations for patient blood management and treatment of anemia are explored. The main conclusion of this review emphasizes that the decision to transfuse RBCs is complex and depends on the interaction between multiple factors including the balance between the risk of anemia and the risk of RBC transfusion, existing patient comorbidities, and medical and surgical exposures. The transfusion thresholds recommended by current

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guidelines vary for medical and surgical patient populations. Guidelines suggesting specific transfusion thresholds for different patient populations should be viewed as a starting point for making an informed decision about RBC transfusion. Alternatives to transfusion (i.e., patient blood management), biomarkers of anemia-induced tissue hypoxia, and transfusion alternatives should continue to be evaluated in large RCTs, with the goal of improving event-free survival in critically ill and perioperative patients.

Résumé Ce compte rendu narratif évalue de façon critique les données probantes concernant le risque de l'anémie et de la transfusion d'érythrocytes. Pour ce faire, nous avons évalué des études randomisées contrôlées (ERC) prospectives de grande envergure réalisées auprès de populations de patients médicaux, chirurgicaux et de soins intensifs dans lesquelles l'impact de seuils spécifiques de transfusion d'hémoglobine est comparé. Dans ces études, les risques de l'anémie sont comparés aux risques de la transfusion d'érythrocytes. Les résultats des comptes rendus systématiques et méta-analyses publiés sont également présentés. Enfin, les recommandations concernant la gestion du sang des patients et le traitement de l'anémie sont explorées. La conclusion principale de ce compte rendu souligne que la décision de transfuser des érythrocytes est complexe et dépend de l'interaction de plusieurs facteurs, notamment de l'équilibre entre le risque de l'anémie et le risque de la transfusion d'érythrocytes, les comorbidités existantes du patient, et les risques médicaux et chirurgicaux. Les seuils de transfusion recommandés par les directives actuelles sont différents pour les populations de patients médicaux et chirurgicaux. Les directives proposant des seuils de transfusion spécifiques en fonction des différentes populations de patients devraient être considérées comme point de départ pour prendre une décision informée concernant la transfusion d'érythrocytes. Les alternatives à la transfusion (c.-à-d. la gestion du sang des patients), les biomarqueurs d'une hypoxie tissulaire induite par l'anémie et les alternatives à la transfusion devraient continuer à être évalués dans des ERC d'envergure, avec pour but l'amélioration de la survie sans complication des patients en état critique et périopératoires.

This narrative review assesses the balance of risks associated with anemia and acute blood loss *vs* those of red blood cell (RBC) transfusion and other treatments for anemia (Fig. 1). Both anemia and transfusion are associated with adverse clinical outcomes including increased mortality.[1–10] Nevertheless, the potential direct causal links between anemia, RBC transfusion, adverse outcomes, and the potential interaction between anemia and transfusion are incompletely understood. Firstly, this

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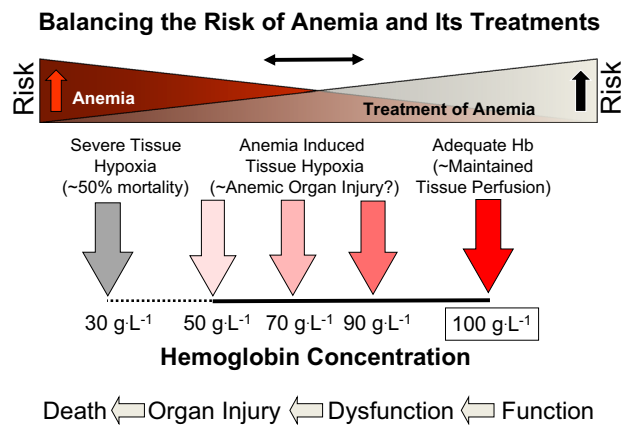
Balancing the Risk of Anemia and Its Treatments

Fig. 1 A model to describe the risks of anemia and its treatment at varying hemoglobin concentrations. These risks are low at hemoglobin concentrations >100 g·L⁻¹, and with decreasing hemoglobin levels, there is an increased risk of dysfunction and organ injury. The point at which the risk of anemia is balanced with the risks associated with red blood cell transfusion remains undefined, as outlined in the manuscript. Modified with permission from Nalla et al.[12]

review will assess the adverse effects of anemia by summarizing the reported risk of anemia in major clinical trials, meta-analyses, and translational studies. Important outcomes will include organ injury and mortality associated with acute and chronic anemia. As RBC transfusion remains one of the main treatments of acute and chronic anemia in critical care and perioperative settings, the potential risk of RBC transfusion will be assessed utilizing retrospective analyses and prospective randomized-controlled trials (RCTs). The rationale for

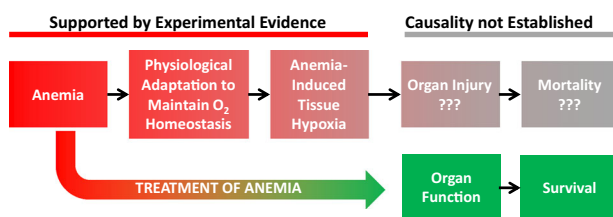### Does Treatment of Anemia Prevent Organ Injury and Mortality?

Fig. 2 Anemia-induced tissue hypoxia may be a common unifying mechanism for organ injury and mortality. It remains undefined whether treatment of anemia restores tissue oxygen delivery, maintains cellular oxygen homeostasis, and prevents organ injury and mortality. There is evidence supporting inadequate physiologic adaptations to anemia leading to anemia-induced tissue hypoxia. Nevertheless, the causality between anemia-induced tissue hypoxia and organ injury and subsequent mortality has yet to be established.

proposed restrictive and liberal transfusion approaches will be reviewed within the context to determine the optimal transfusion thresholds in different patient populations. We then look at options for ameliorating the risk associated with both anemia and transfusion including patient blood management and anemia treatment algorithms, and assess the potential for treatment of anemia to avoid the adverse outcomes associated with anemia and RBC transfusion[11–13] (Fig. 2).

The over-arching objective of this review is to understand that recommendations for hemoglobin (Hb) transfusion thresholds remain generally restrictive; however, the degree of restriction varies depending on the patient comorbidities and critical care or surgical exposure. Current RCTs are exploring the potential benefit or harm of more liberal transfusion thresholds in specific patient populations. Recommendations for Hb thresholds are a starting point for transfusion decisions, which should incorporate additional patient-specific factors to optimize patient care.

Defining anemia

An estimated 80% of our body's cells are RBCs[14] and Hb comprises the main component of RBC content. This emphasizes the importance of RBCs as the vehicle for Hb to carry oxygen and facilitate its effective delivery to peripheral tissues. Anemia is defined as a decreased number of RBCs and a reduced Hb concentration in the blood. Chlorosis (Greek for "green") was an early term used to describe patients with anemia based on the patient's appearance and skin colour.[15] The recent evolution of the diagnosis and treatment of anemia was started by early western physicians such as Thomas Sydenham (England 1624–1689). Sydenham recognized the nutritional basis of anemia and was known to prescribe iron supplementation to treat it (e.g., "iron filings steeped in cold Rhenish wine").[15] Yet, despite decades of attention from the modern medical community, our knowledge of the pathophysiology and treatment of anemia remain incomplete. Anemia is defined by the World Health Organization as a Hb < 130 g·L⁻¹ in men and < 120 g·L⁻¹ in women.[16] Anemia is a major global health burden, affecting approximately one third of the world's population.[17,18] While beyond the scope of this review, anemia is a leading cause of *global years lived with a disability* in young adults[19] and has been associated with morbidity and mortality in patients of all ages (including neonates and children,[20] pregnant women,[21] adults, and the elderly.[17–19,22]

What are the risks associated with perioperative anemia?

Within this section, we will review the risk to patients with pre-existing (i.e., chronic) anemia (largely due to iron deficiency or iron restriction), and the impact of acute anemia associated with acute surgical bleeding and fluid resuscitation. It is clear that both types of anemia may interact to contribute to adverse outcomes.

The risk of preoperative anemia

The adverse impact of anemia on perioperative outcomes has been previously reviewed.[1,5,10,23] Recently published outcome data from the International Surgical Outcomes Study (ISOS) trial and other databases show that the prevalence of perioperative anemia remains high (approximately 30–40%) in patients undergoing surgery.[17,24,25] The incidence of anemia is comparable (approximately 30%) in patients undergoing cardiac surgery.[26] In both types of surgery, anemia is an independent risk factor for increased short- and long-term mortality.[17,24,25,27,28] In these retrospective clinical studies, the presence of perioperative anemia has been associated with adverse outcomes including acute renal failure,[5,6,24,25,28] myocardial infarction (MI),[4,29] stroke,[5,6,28] and increased mortality.[1,17,24,25,27,28,30] In a recent meta-analysis by Fowler *et al.*,[24] an association was found between pre-surgical anemia, postoperative acute kidney injury (AKI), stroke, death, and infection. In addition, Fowler *et al.*[17] found that the risk of mortality and complications increased with worsening anemia in patients admitted for elective inpatient surgery, especially postoperative infection.

Anemic patients, when compared with non-anemic patients, were more likely to require treatment in the intensive care unit (ICU) and have a longer in-hospital stay.[17] Lastly, investigators found that high income countries experienced fewer complications in their anemic patients than low to medium income countries, suggesting that anemia may be of greater concern in the latter.[17] The mechanism by which anemia in surgical patients increases morbidity and mortality has not been established but the take home message is simple—anemia is associated with an increase in morbidity and mortality in patients undergoing surgery or with critical illnesses.

The risk of acute intraoperative anemia and hemodilution

Intraoperative acute anemia is a common event most often related to acute blood loss and/or concurrent hemodilution with intravenous fluids. This disruption of physiologic hemodynamics has been extensively modeled and studied in animal experiments.[31–35] In surgical patients, the two patient populations who commonly suffer from moderate to severe acute hemodilution in the perioperative context are those who refuse transfusions for religious reasons[1,2,4] and those undergoing cardiopulmonary bypass (CPB) for cardiac surgery.[3,6,36,37] In these and other populations, acute hemodilutional anemia has been associated with worsened patient morbidity and mortality.[1–6,36] In translational animal models, acute and subacute anemia increased expression of markers for tissue hypoxia, thus providing a possible causal link between anemia, tissue hypoxia, organ injury, and death (Fig. 2).

Animal models of acute and subacute anemia have identified several important concepts for understanding anemia. These include the finding that acute anemia leads to tissue hypoxia in vital organs including the brain, kidney, and liver.[32,34,35,38] In addition, inhibition of active cardiovascular response to acute anemia by preventing the increase in cardiac output and cerebral vasodilation with β1 and β2 specific antagonists accentuated anemia-induced cerebral-tissue hypoxia.[31,39–41] Further support for the importance of adaptive hypoxic cellular responses during anemia are provided by studies in which genetic deletion of neuronal nitric oxide synthase (nNOS) inhibited the molecular response of hypoxia signalling to anemia.[34] Mice deficient in nNOS exhibited a severely attenuated hypoxic cellular response to acute anemia, and did not show the characteristic real-time increase in hypoxia-inducible factor-α normally observed in living transgenic hypoxia-inducible factor (HIF)-luciferase mice.[34] These nNOS deficient mice also lacked the cardiac output response to acute anemia. Absence of these adaptive cellular and cardiovascular responses may have contributed to the observed increase in acute mortality in acutely anemic rodents.[34] Thus, animal models of acute and subacute anemia show that anemia leads to tissue hypoxia despite the simultaneous activation of adaptive integrative physiologic responses to maintain tissue oxygen delivery. Inhibiting these responses increased the severity of tissue hypoxia[31,40,41] and increased mortality.[34]

The impact of acute surgical blood loss resulting in anemia in patients who decline RBC transfusion has been extensively reviewed. These studies showed a direct relationship between decreasing Hb and mortality.[1,2,4] An acute reduction in Hb to 30 $g \cdot L^{-1}$ leads to about a 50% mortality rate with an increase towards 100% mortality as Hb decreases further (Fig. 1).[1,2,4,10] The mechanisms of death likely include the loss of blood oxygen-carrying capacity to a level that cannot support sufficient tissue oxygen delivery to maintain cellular energetics and biological function.

In addition, acute hemodilution during cardiac surgery involving CPB, as well as lowest hematocrit (Hct) on CPB, have been associated with worsened perioperative morbidity, including stroke,[36,42] AKI,[36,43,44] and MI,[36] and to increased mortality.[3,5,6,36] The relationship between nadir Hct and perioperative stroke was clearly shown by Karkouti *et al.* who found an increased incidence of stroke with a declining nadir Hct on CPB.[42] This correlation was possibly related to the increase in cerebral blood flow associated with acute anemia on CPB,[45] which may have increased the number of emboli directed to the brain, and/or anemia-induced brain tissue hypoxia[32] may have accentuated the negative impact of any single embolic event.[46] With respect to AKI associated with CPB, retrospective studies have shown a relationship between intraoperative hemodilutional anemia while on CPB and postoperative renal dysfunction (Fig. 3).[36,37,43,44] Karkouti *et al.* also showed that AKI is associated with an increase in mortality in patients who experience a significant reduction in estimated glomerular filtration rate or a need

for dialysis within one week of cardiac surgery.[44] Modifiable risk factors for AKI include both preoperative anemia and perioperative transfusion. The importance of the impact of AKI on patients undergoing CPB was emphasized by a recent meta-analysis that showed a correlation between AKI, duration of CPB, and increased mortality.[47]

A possible explanation for this relationship between anemia, CPB, and renal injury could relate to the kidney's susceptibility to low tissue oxygen delivery, and the impact of acute hemodilution on reducing renal tissue partial pressure of oxygen (PO_2) during conditions of non-physiologic perfusion on CPB.[48–51] Tissues in the region of the medulla of the kidney have lower partial pressures of oxygen relative to the renal cortex, both at baseline and following acute anemia,[49] likely because of a lower oxygen supply relative to the higher metabolic demand in the medulla. The impact of anemia on renal medullary hypoxia is accentuated in rats undergoing CPB[50] and has been associated with an increase in endothelial nitric oxide

Anemia-Induced Renal Hypoxia as a Potential Mechanism for Acute Kidney Injury (AKI)

Moderate Anemia (Hb ~90g/L) is Associated with Renal Hypoxia in Mice
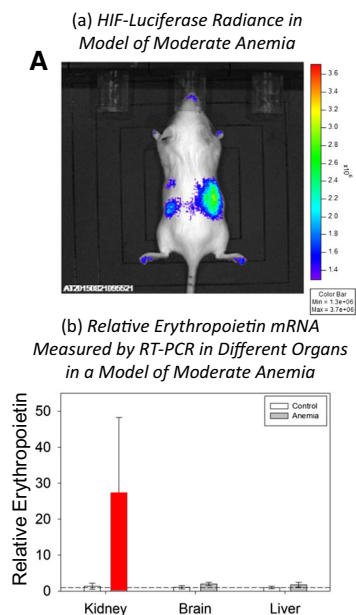
Evidence of Renal Hypoxia and AKI in Anemic Patients on Cardiopulmonary Bypass
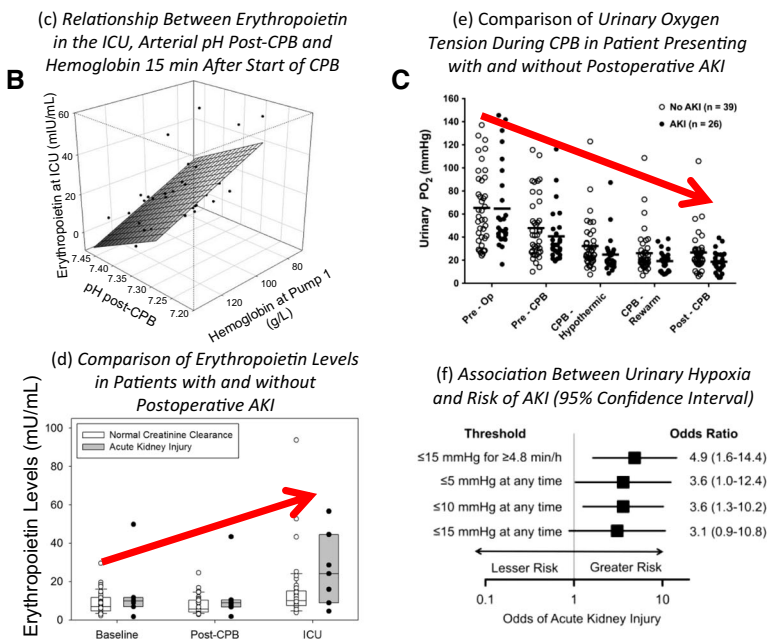
Fig. 3 Anemia-induced renal hypoxia as a potential mechanism for acute kidney injury (AKI). A) Experimental models of moderate anemia have been associated with a high magnitude of renal hypoxia as evidenced by increased hypoxia-inducible factor luciferase radiance (a) and erythropoietin mRNA levels (b). B) Observational studies have associated acute early anemia on cardiopulmonary bypass with renal hypoxia as evidenced by delayed increase in erythropoietin expression upon intensive care unit admission (c) and (d). C) Prospective studies have shown a reduction in urinary oxygen tension with cardiopulmonary bypass (e). The duration and magnitude of urinary hypoxia has been associated with a greater risk of postoperative acute kidney injury (f). Adapted with permission from Mistry *et al.*,[38] Hare *et al.*,[54] and Zhu *et al.*[53]

synthase expression within the renal medulla (not renal cortex) of anemic rats following CPB.[51] A more pronounced decrease in oxygen delivery associated with hemodilution, and non-physiologic perfusion on CPB could further disrupt the oxygen delivery-consumption balance, resulting in renal hypoxia and tissue injury.[52,53] A recent clinical trial showed an association between acute anemia, metabolic acidosis, and increased systemic erythropoietin (EPO) levels (response to renal hypoxia),[54] further supporting a potential causal link between anemia-induced tissue hypoxia and organ injury.

The previous relationships between acute anemia and adverse outcomes including AKI do not provide evidence of causality. It is reasonable to believe that multiple factors associated with hemodilution in both the above-mentioned populations could be involved in increased perioperative morbidity and mortality, such as hypotension, hypoperfusion, effect of anesthesia,[55] and the artificial circulation associated with CPB.[56] In the case of CPB,[37] circulatory dynamics directly related to the CPB apparatus, and changes in rheology during acute hemodilution may negatively affect renal tissue PO_2.[50] In addition, translational studies that have assessed hypoxia signalling mechanisms in the kidney during acute anemia support the hypothesis that inadequate oxygen delivery to tissues could contribute to organ failure and mortality during acute anemia.[31,35,38,53,57]

As seen in murine models, moderate anemia is associated with renal hypoxia as shown by an increase in HIF in the kidney.[31,34,35,38] Such molecular hypoxia signalling is a primary function of the kidney under physiologic conditions. Increased production of the HIF-dependent molecule EPO in the kidney as well other organs is a physiologic responses to correct anemia.[58,59] The physiologic EPO response to anemia-induced tissue hypoxia occurs in greatest magnitude in the kidney (approximate 20-fold increase in RNA level) relative to other tissues such as the brain (approximate two-fold increase in RNA level).[38] In addition, EPO is more sensitive in terms of magnitude of response to tissue hypoxia relative to other HIF-dependent molecules.[38,48] Nevertheless, if the anemia-induced renal hypoxia is severe and prolonged, this exposure may lead to much higher expression and release of renal EPO and eventually lead to renal tissue injury.[53] A recent study in humans undergoing CPB supports this hypothesis by showing that low Hb was associated with increased lactic acid and a subsequent increase in EPO levels in the ICU. Patients who developed AKI (KDIGO criteria; increase in serum creatinine > 26.5 $umol \cdot L^{-1}$ within 48 hr of surgery or > 1.5 times the baseline value within seven days of surgery) showed a numerical trend towards higher EPO levels in the ICU ($P = 0.08$) compared with non-AKI counterparts, indicating

possible worse renal hypoxia.[54] Additional evidence that renal hypoxia is associated with kidney injury is provided by a human study showing that prolonged reductions in renal/urinary PO_2 is associated with kidney injury[53] (Fig. 3). Nonetheless, further study will be required to prove causality and to determine if treatment of anemia can avert this outcome.

What is the risk associated with RBC transfusion?

While the actuarial risk of immediate mortality associated with RBC transfusion is of the same order of magnitude as being struck by lightning,[60–62] real concerns about morbidity and mortality exist. Transfusion risks are routinely reported by established reporting agencies including the US Food and Drug Association (FDA),[63] the National Healthcare Safety Network Hemovigilance Module in the US,[64] the UK's Serious Hazards of Transfusion (SHOT) program,[62] and the Canadian Transfusion Transmitted Injuries Surveillance System (TTISS).[65]

According to the UK National Health Service SHOT annual report on transfusion-related adverse events,[62] human error is an important factor for a high proportion (87.3%) of transfusion-related adverse outcomes. These include ABO incompatibility events, incorrect blood component transfusions, handling and storage errors, delayed transfusion, avoidable transfusion, over- and under-transfusion, "right blood type (wrong blood) to right patient-type" errors (a circumstance when the patient was transfused with the right blood type despite errors in identifying the correct patient or blood unit), and near misses. The near-misses category accounted for 43.6% of reported adverse events.[62] A large proportion of major adverse reactions include transfusion-associated circulatory overload (TACO), febrile responses, and allergic and hypotensive reactions. With regard to transfusion-related deaths, over the past nine years, the leading causes of death were pulmonary complications including transfusion-related lung injury (TRALI) and respiratory complications secondary to TACO. Transfusion-associated circulatory overload is reported as one of the leading cause of transfusion-related mortality and major morbidity in the UK.[62]

According to FDA reports in 2017 and 2018, TACO remains one of the most common causes for transfusion-related mortality in the United States. Consistent with this, in Canada's TTISS 2006–2012 report, up to 42% of adverse reactions related to blood component transfusion were classified as TACO. While severe allergic anaphylactic/anaphylactoid reactions accounted for 14% of transfusion-related reactions. During this same period,

TACO was also associated with 32% of deaths related to transfusion. Interestingly, the incidence/risk of TACO and TRALI are often not specifically reported in RCTs assessing the impact of liberal *vs* restrictive transfusion thresholds.[66–68]
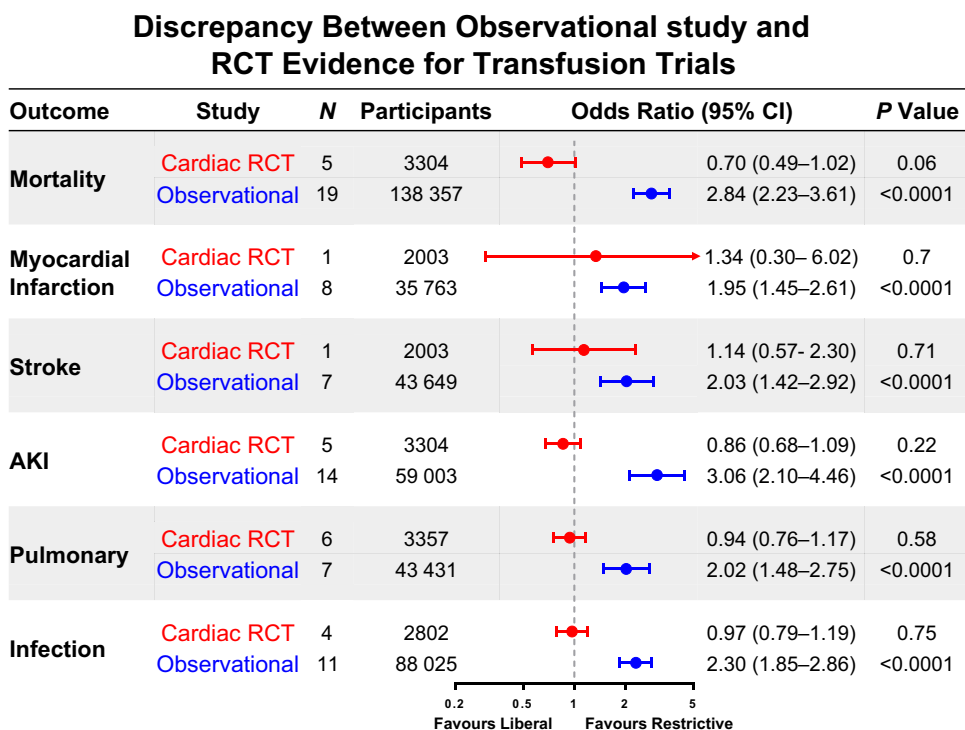
Finally, ongoing data published by the ONTraC network in Ontario have shown that a reduction of RBC transfusion through patient blood management programs has significantly reduced transfusion-related adverse events.[11,13,69] As shown by Yanagawa *et al.* in patients presenting for cardiac surgery,[13] increasing severity of anemia is associated with an increase in the number of RBC transfusions. This increase in RBC transfusion in more anemic patients shows a possible confounding—i.e., "sicker" and more anemic patients receive more transfusions and therefore are exposed to the increased risks of transfusion. Thus, adverse outcomes associated with anemia and RBC transfusion are linked.[10] Retrospective data have shown that the risk of adverse outcomes, including death, increases as a function of the number of units transfused.[8,9,70] If the risks associated with transfusion make clinicians reticent to transfuse RBCs in acute clinical situations, then the risks associated with untreated acute blood loss and anemia must be considered. For example, the 2018 SHOT report states 112 reports of delayed transfusion (3.3% of total reports) were associated with adverse outcomes including death, marking the importance of the timely and effective treatment of acute anemia.[62] Thus, hesitancy to transfuse based on the belief that all patients should have a restrictive transfusion threshold may cause harm in conditions associated with acute or active blood loss.

What is the risk of transfusion specifically in critically ill and surgical patients?

Much of the concern about adverse outcomes associated with RBC transfusion is informed from observational (retrospective) data[8,9] as opposed to prospective RCTs.[70] Observational data often report a high odds ratio (OR) for adverse clinical outcomes associated with transfusion including mortality, MI, stroke, AKI, pulmonary morbidity, and infection (Fig. 4).[8,9,70] For example, in a retrospective study, Koch *et al.* found that, in patients undergoing coronary artery bypass grafting, each unit of RBC transfused was associated with incremental risks of postoperative morbidity and mortality. These risks had notably high ORs for mortality, renal failure, prolonged ventilatory support, serious infection, cardiac complications, and neurologic events.[9] Also favouring transfusion avoidance are two large multicentre observational studies in critical care—the anemia and blood transfusion in the critically ill-current clinical practice in the United States (CRIT) study in North America,[71] and the Anemia and Blood transfusion in the Critically ill (ABC) study in Europe[72]—which both suggested that RBC transfusion was independently

Fig. 4 Discrepancy between evidence from randomized-controlled trials *vs* observational trials assessing adverse outcomes in transfusion threshold trials. Odds ratios compare the liberal strategy with the restrictive strategy. Adapted with permission from Patel *et al.*[70]

Discrepancy Between Observational study and RCT Evidence for Transfusion Trials

Outcome	Study	N	Participants	Odds Ratio (95% CI)	P Value
Mortality	Cardiac RCT	5	3304	0.70 (0.49–1.02)	0.06
	Observational	19	138 357	2.84 (2.23–3.61)	<0.0001
Myocardial Infarction	Cardiac RCT	1	2003	1.34 (0.30–6.02)	0.7
	Observational	8	35 763	1.95 (1.45–2.61)	<0.0001
Stroke	Cardiac RCT	1	2003	1.14 (0.57–2.30)	0.71
	Observational	7	43 649	2.03 (1.42–2.92)	<0.0001
AKI	Cardiac RCT	5	3304	0.86 (0.68–1.09)	0.22
	Observational	14	59 003	3.06 (2.10–4.46)	<0.0001
Pulmonary	Cardiac RCT	6	3357	0.94 (0.76–1.17)	0.58
	Observational	7	43 431	2.02 (1.48–2.75)	<0.0001
Infection	Cardiac RCT	4	2802	0.97 (0.79–1.19)	0.75
	Observational	11	88 025	2.30 (1.85–2.86)	<0.0001

0.2　0.5　1　2　5
Favours Liberal　Favours Restrictive

associated with mortality after adjusting for confounders. It is unclear, though, whether the increased mortality can be explained by residual (i.e., unaccounted for) confounding. Again, there is discrepancy between the high ORs for risk of transfusion in observational studies, which are associated with possible confounding factors, *vs* prospective RCTs, where such confounding can be minimized. In one analysis, the risk of transfusion in liberal *vs* restrictive transfusion strategies are much closer to unity, emphasizing the importance of assessing the outcomes of prospective RCTs (Fig. 4).

The reason for the discrepancy in risk of transfusion reported by retrospective *vs* prospective studies may derive from confounding associated with clinical practice for acutely ill patients. In this setting, patients who are assessed as doing poorly clinically may receive a blood transfusion as part of their care plan. Nevertheless, the blood transfusion may be unrelated to the disease pathophysiology responsible for adverse outcomes. In this setting, adverse outcomes may occur because of the disease, and be independent to RBC transfusion. Nevertheless, the outcomes become statistically linked to the RBC transfusion even though the transfusion may not have impacted outcome, thus inappropriately attributing risk to the transfusion.

What do the current RCTs tell us?

With an expanding number of large well-conducted transfusion RCTs, systematic reviews and clinical guidelines that confirm the relative benefits of restrictive and liberal transfusion strategies seem to be highly dependent on the patient population, study design, and surgical risk.[23,73,74] The synthesis of these trial results suggest that all critically ill patients should be transfused using a restrictive transfusion threshold of 70 g·L^{-1}.[75] The original findings of the Transfusion Requirements in Critical Care (TRICC) trial did not show a significant difference between liberal and restrictive transfusion in terms of 30-day mortality (the primary outcome) ($P = 0.11$). Interestingly, the secondary outcomes supported the hypothesis that restrictive transfusion may be superior in specific subpopulations, such as younger, less ill patients, as mortality was lower in the restrictive transfusion group in patients < 55 years old ($P = 0.02$) and with an Acute Physiology And Chronic Health Evaluation II score ≤ 20 ($P = 0.02$).[76] Furthermore, additional sub-analyses of this trial revealed that patients with cardiovascular disease or traumatic brain injury tended to have better outcomes with a more liberal transfusion threshold.[77,78] Thus, this landmark study suggests that different patient subpopulations may benefit from a more liberal or a more restrictive transfusion strategy, depending on patient

comorbidities and clinical conditions. Additionally, data sets from the Transfusion Requirements in Cardiac Surgery III (TRICS III) study support an interesting hypothesis regarding liberal *vs* restrictive transfusion.[66,73] In this study assessing restrictive *vs* liberal transfusion strategies in cardiac surgical patients, most subgroup analyses showed no interaction of demographic factors with the primary outcome. Nevertheless, stratification of subjects by age suggested that older patients may benefit from a restrictive transfusion strategy, while younger patients may benefit from a more liberal transfusion strategy[66,73] (Fig. 5). This has led to the proposed TRICS IV study (ClinicalTrials.gov; NCT02042898), which will test the hypothesis that a liberal transfusion strategy is superior to a restrictive strategy in younger patients undergoing cardiac surgery.

Should we consider a universal transfusion threshold or a spectrum of transfusion thresholds for different patient populations and clinical conditions?

In considering the statement: "*A transfusion threshold of 70 g·L^{-1} should be the new norm […] for all critically ill patients. […] We recommend upgrading the evidence base […] to class 1A (strong recommendation and evidence)*[75]", written by Drs Hébert and Carson in a 2014 editorial in the New England Journal of Medicine, we need to explore the relative importance of the stated protocol transfusion threshold *vs* the Hb range to which the randomized patients are actually exposed to during the study (the average/or lowest daily Hb). Many physicians withhold transfusion until a threshold of 70 g·L^{-1} is "triggered", leaving patients at a Hb value near 70 g·L^{-1} without transfusion. As shown in the summary Figs 6–8, on average, patients in the restrictive arms have Hb levels that are often well above the stated trigger *per se*. In these Figures, trials have been selected based on their sample size and prospective randomized design and grouped based on similar procedures and patient populations.[74] Exclusion criteria for these include small sample size ($n \leq 100$), lack of Hb results, or stratification of transfusion triggers. The most recent transfusion guidelines for the recommended thresholds have been based on the largest current trials as they carry the most weight in current scientific knowledge.[23] While the trial design does not differentiate between transfusion and no transfusion, the paradigm set forth since the original TRICC trial involves comparing a restrictive transfusion strategy to a more liberal strategy in an attempt to define best practice in transfusion. To assess the impact of restrictive *vs* liberal transfusion strategies on clinical outcomes, data were extracted from well-conducted large RCTs in three patient populations

Six Month Outcomes after Restrictive vs. Liberal Transfusion For Cardiac Surgical Patients (TRiCSIII)

Subgroup		N		P Value for Interaction
Age	<45 years	102		0.004
	45 – 54 years	172		
	55 – 64 years	507		
	65 – 74 years	1556		
	75 – 84 years	2108		
	85+ years	219		
Sex	Female	1631		0.822
	Male	3033		
Diabetes	No	3391		0.307
	Yes	1273		
Creat Clearance	≥ 50mL/min	3849		0.907
	< 50mL/min	813		
Pulm Disease	No	3888		0.858
	Yes	776		
Surgery	CABG Only	1218		0.744
	Non-CABG	2161		
	CABG+ Other	1285		
LV Function	Good	2887		0.845
	Moderate	1378		
	Poor	314		
	Very Poor	83		
Preop Hb	<120g/L	1083		0.730
	≥120g/L	3580		

0.2   0.5   1   2   5

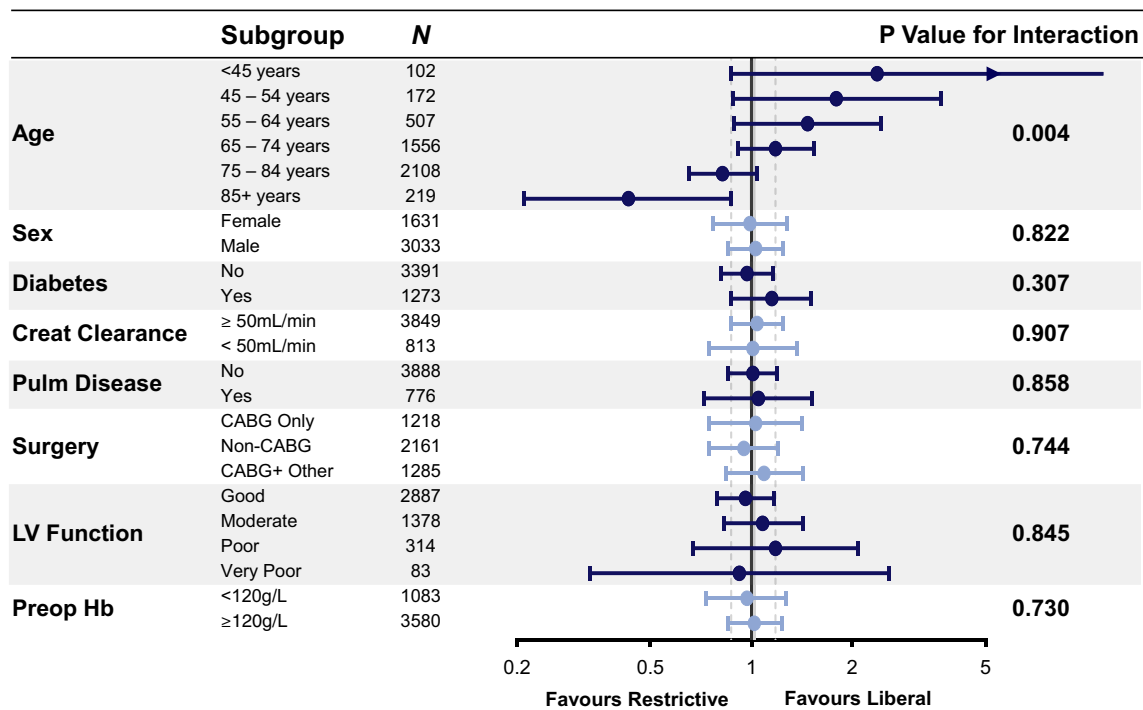Favours Restrictive   Favours Liberal

Fig. 5 Unadjusted subgroup analyses of primary outcome. Odds ratios compare the restrictive strategy with the liberal strategy. The solid and dashed grey lines represent the odds ratio and 95% confidence interval for the primary composite outcome of death, stroke, myocardial infarction, and renal failure requiring dialysis at six months from index surgery. Adapted with permission from Mazer et al.[73]

including: 1) medical patients with critical illness,[76,79–83] 2) patients with cardiovascular risk undergoing orthopedic surgical procedures,[67,84,85] and 3) patients undergoing cardiac surgery.[66,68,86–88] Data for Hb concentration, at or near discharge (representing the clinical exposure), were extracted and compared with the listed primary outcomes reported most frequently at 28–90 days postoperatively (Table 1).

Transfusion threshold in the critically ill patient

The concept of comparing restrictive and liberal transfusion strategies originated with the critical care trial led by Hébert et al. assessing whether it was safe to restrict transfusion in critically ill patients to 70 g·L^{-1}. The trial results showed no difference in the primary outcome of mortality between the two groups, suggesting that restrictive transfusion can be safely applied to the sickest patients.[76] The Transfusion Requirements in Septic Shock (TRISS) trial in 2014 supported this finding and led to a fundamental paradigm shift in clinical care—i.e., that a restrictive transfusion threshold is the new norm.[81] Nevertheless, apart from the original TRISS trials in

which the average Hb level in the restrictive arm actually approaches the administrative trial threshold of 70 g·L^{-1}, in all other medical trials, randomization to the restrictive arm resulted in an average Hb concentration above 80 g·L^{-1} (Fig. 6). In addition, a growing number of well-conducted trials in diverse surgical patient populations suggest that a one threshold fits all approach may not be optimal.

Transfusion threshold in the orthopedic surgical patient with cardiovascular risk

Review of three large trials showed that the mean daily Hb in the restrictive arms in patients undergoing orthopedic procedures were all above 90 g·L^{-1} (Fig. 7). In the 2011 Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial, liberal vs restrictive transfusion practices were assessed in high risk patients (i.e., patients with cardiovascular disease or cardiovascular risk factors) after hip surgery, where the primary outcome was death or the ability to walk across a room without assistance after 60 days. The conclusion of this trial was that the restrictive

Restrictive Transfusion Thresholds and Restrictive Hemoglobin Range in Critically Ill Patients
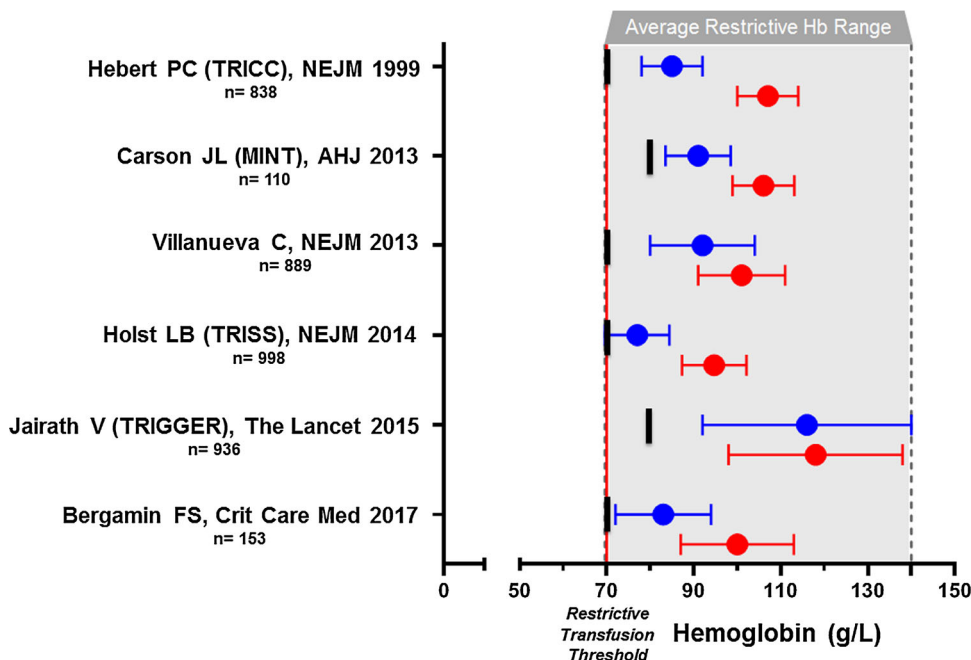

Fig. 6 Restrictive transfusion thresholds and restrictive hemoglobin range (range of last measured hemoglobin before discharge in the restrictive arm) for trials assessing critically ill patients. Black bars indicate the protocol specific restrictive transfusion trigger for each representative trial. The mean and standard deviation (SD) represents the last or pre-discharge hemoglobin level for each representative trial. Red indicates liberal treatment group, and blue indicates restrictive treatment group. The restrictive hemoglobin range (in grey) is represented by the lowest bound of the SD of the lowest restrictive treatment group, and the highest bound of the SD of the highest restrictive treatment group. The guideline recommended restrictive red blood cell transfusion threshold suggests transfusion at a threshold in the critically ill is of 70 g·L^{-1} (red line).[23] Data extracted from published trials.[76,79–83]

threshold of 80 g·L^{-1}, (not 70 g·L^{-1}) was non-inferior to 100 g·L^{-1}. Nevertheless, when reviewing outcome data, 156 vs 53 patients ($P < 0.001$) in the restrictive vs liberal group respectively received blood transfusion for clinical indications such as for treatment of hypotension, tachycardia, congestive heart failure, chest pain, or rapid bleeding. Thus, a difference of 103 patients in the restrictive arm vs liberal arm (approximately 10% of the group sample size) received more liberal transfusions than they would have based solely on the Hb threshold. Had these patients not received these transfusions, the outcome data analysis may have been different.[67] This trial supports the addition of physiologic or functional variables as a component of the outcome analysis.

Transfusion threshold in the cardiac surgical patient

For patients undergoing cardiac surgery, clinicians have long held strong opinions about the Hb threshold or trigger used to optimally manage their patients. Murphy et al. provided data that maintained equipoise between restrictive and liberal transfusion strategies following publication of

the Transfusion Indication Threshold Reduction (TITRe2) trial (Fig. 8). In that study, patients undergoing cardiac surgery were randomized to restrictive or liberal protocols after cardiac surgery. While there was no difference in the primary outcome (a composite of mortality, ischemic event, and serious infection or ischemic event within three months after surgery), an important secondary outcome was observed—i.e., a significant difference in 90-day mortality that favoured liberal transfusion.[68] The TRICS III trial again showed non-inferiority of restrictive vs liberal strategy at 90 days and six months.[66,73] While the primary outcome data and subsequent six-month outcome data showed non-inferiority of a restrictive transfusion strategy in all patients, some interesting observations were made. A sub-analysis did not show any interaction of transfusion strategy with important comorbidities, including preoperative Hb, left ventricular function, type of surgery, pulmonary disease, diabetes, or sex. Nevertheless, the analyses did show a significant age interaction (Fig. 5). The primary outcome, when stratified by age, showed an interaction where a restrictive transfusion strategy was favoured in patients ≥ 75 yr

Table 1 Summary of transfusion threshold studies

	Patient population	Transfusion threshold	Last available Hb measurement during hospital stay (mean ± SD; g·L^{-1})	Time-point of last available Hb measurement	Primary outcome	Point estimate for primary outcome[a] (95% CI)
Critically ill patients						
Hebert PC (TRICC), NEJM 1999[76]	Critically ill patients with euvolemia	R: Hb <70 g·L^{-1}	85 ± 7	Average daily hemoglobin concentration	Mortality at 30 days	ARD: − 4.7% (− 10.2% to 0.84)[b]
		L: Hb <100 g·L^{-1}	107 ± 7			
Carson JL (MINT), AHJ 2013[80]	Anemic patients with acute coronary syndrome or stable angina undergoing cardiac catherization	R: Hb <80 g·L^{-1}	91 ± 8	3 days after randomization	Composite of mortality, MI, or coronary revascularization at 30 days	ARD: 15.0% (0.70% to 29.3)
		L: Hb <100 g·L^{-1}	106 ± 7			
Villanueva C, NEJM 2013[83]	Severe acute upper gastrointestinal bleeding	R: Hb <70 g·L^{-1}	92 ± 12	At discharge	Mortality at 45 days	HR: 0.55 (0.33 to 0.92)
		L: Hb <90 g·L^{-1}	101 ± 10			
Holst LB (TRISS), NEJM 2014[81]	Septic shock	R: Hb ≤70 g·L^{-1}	77 ± 7	28 days after randomization	Mortality at 90 days	RR: 0.94 (0.78 to 1.09)
		L: Hb ≤90 g·L^{-1}	94 ± 7			
Jairath V (TRIGGER), Lancet[82] 2015	Acute upper gastrointestinal bleeding	R: Hb <80 g·L^{-1}	116 ± 24	Last Hb before discharge	Feasibility and exploratory clinical outcomes at hospital discharge/28 days	NS for clinical outcomes[c]
		L: Hb <100 g·L^{-1}	118 ± 20			
Bergamin FS, Crit Care Med[79] 2017	Cancer patients with septic shock	R: Hb <70 g·L^{-1}	84 ± 11	Day 7 after ICU admission	Mortality at 28 days	HR: 1.35 (0.96 to 1.89)[b]
		L: Hb <90 g·L^{-1}	100 ± 13			
Orthopedic surgical patients with CV risk						
Grover M, Vox Sang 2006[85]	Elderly patients undergoing elective lower limb arthroplasty	R: Hb <80 g·L^{-1}	98 ± 12.3	5 days postoperative	Silent myocardial ischemia at 72 hr after surgery	ARD: − 4.6% (− 15.5% to 6.0)
		L: Hb <100 g·L^{-1}	111 ± 9.3			
Carson, JL (FOCUS) NEJM[67] 2011	Anemic patients at high CV risk undergoing hip-fracture surgery	R: Hb <80 g·L^{-1}	97 ± 9	7 days after randomization	Death or inability to walk independently at 60 days	ARD: − 0.50% (− 4.7% to 3.7)[b]
		L: Hb <100 g·L^{-1}	111 ± 9			
Gregersen M (TRIFE), Acta Orthop 2015[84]	Frail elderly patients undergoing hip fracture surgery	R: Hb <97 g·L^{-1}	120 ± 12	30 days postoperative	Recovery from physical disability outcomes at 90 days	NS for recovery from disability outcomes[d]
		L: Hb <113g·L^{-1}	128 ± 9			
Cardiac surgical patients						
Bracey AW, Transfusion 1999[86]	Elective coronary artery bypass graft surgery	R: Hb <80 g·L^{-1}	94 ± 9	6 days postoperative	Clinical outcomes including mechanical ventilation, hospital stay, morbidity, and mortality until hospital discharge	NS for clinical outcomes[e]
		L: Hb <90 g·L^{-1}	97 ± 11			

Table 1 continued

	Patient population	Transfusion threshold	Last available Hb measurement during hospital stay (mean $\pm$ SD; g·L^{-1})	Time-point of last available Hb measurement	Primary outcome	Point estimate for primary outcome[a] (95% CI)
Hajjar LA (TRACS), JAMA[87] 2010	Elective cardiac surgery	R: maintain Hct $\geq$24%	91 ± 8	7 days after ICU admission	Composite of mortality and severe morbidity at 30 days	ARD: 1% ($-$ 6 to 4); above the $-$ 8% noninferiority threshold, confirming noninferiority between groups
		L: maintain Hct $\geq$30%	105 ± 8			
Murphy GJ (TITRe2), NEJM[68] 2015	Nonemergency cardiac surgery	R: Hb <75 g·L^{-1}	93 ± 10	30 days after randomization	Composite of serious infection or ischemic event at 3 months	OR: 1.11 (0.91 to 1.34)
		L: Hb <90 g·L^{-1}	102 ± 10			
Koch CG, Ann Thorac Surg[88] 2017	Elective cardiac surgery on CPB	R: Hct <24%	95 ± 13	'The Floor' unit	Composite postoperative morbidity and mortality	OR: 0.86 (0.29 to 2.54)
		L: Hct <28%	102 ± 10			
Mazer CD (TRICS III), NEJM[66] 2017	Moderate-to-high risk patients undergoing cardiac surgery on CPB	R: Hb <75 g·L^{-1}	94 ± 13	Pre-discharge	Composite of mortality, MI, stroke, or new-onset renal failure with dialysis at hospital discharge/28 days	ARD: $-$ 1.11% ($-$ 2.93 to 0.72); within the 3% noninferiority margin, confirming noninferiority between groups (P <0.001 for noninferiority)
		L[f]: Hb <95 g·L^{-1} & <85 g·L^{-1}	102 ± 12			

ARD = absolute risk difference; CI = confidence interval; CPB = cardiopulmonary bypass; CV = cardiovascular; Hb = hemoglobin concentration; Hct = hematocrit; HR = hazard ratio; ICU = intensive care unit; L = liberal strategy; MI = myocardial infarction; NS = not significant; OR = odds ratio; R = restrictive strategy; RR = relative risk.

All randomized-controlled trials are of a superiority design, except for TRACS (Hajjar JAMA 2010) and TRICS3 (Mazer NEJM 2017), which are of a noninferiority design.

[a] All point estimates compare the restrictive threshold group with the liberal threshold group.

[b] This value was converted from a point estimate comparing the liberal threshold group with the restrictive threshold group.

[c] The mean differences and 95% confidence intervals for all clinical outcomes between groups included a risk difference of 0.

[d] The P values for all recovery from physical disability outcomes had a value greater than 0.05.

[e] The authors note no significant difference for all clinical outcomes.

[f] Patients transfused if Hb < 95 g·L^{-1} in the operating room and intensive care unit, and transfused if Hb < 85 g·L^{-1} on the ward.

(OR, 0.77; 95% confidence interval [CI], 0.62 to 0.96) and a liberal transfusion strategy was favoured in younger patients (< 75 yr) (OR, 1.32; 95% CI, 1.07 to 1.64) with respect to the primary composite outcome. This interaction was consistent with deciles of age. This hypothesis-generating data suggested a possible effect by age grouping and has led to a successful Canadian Institutes of Health Research application for the TRICS IV study, which will assess the potential superiority of a liberal transfusion strategy in younger patients undergoing cardiac surgery. Thus, within the data set of the largest transfusion

trial completed to date, patient variability may determine whether restrictive or liberal transfusion is optimal and in which patient population.

Transfusion threshold consensus statement

Based on the collective data from many completed transfusion trials, a 2018 Patient Blood Management Consensus Conference has recommended different transfusion thresholds for a variety of medical and surgical patient populations, with recommendation for
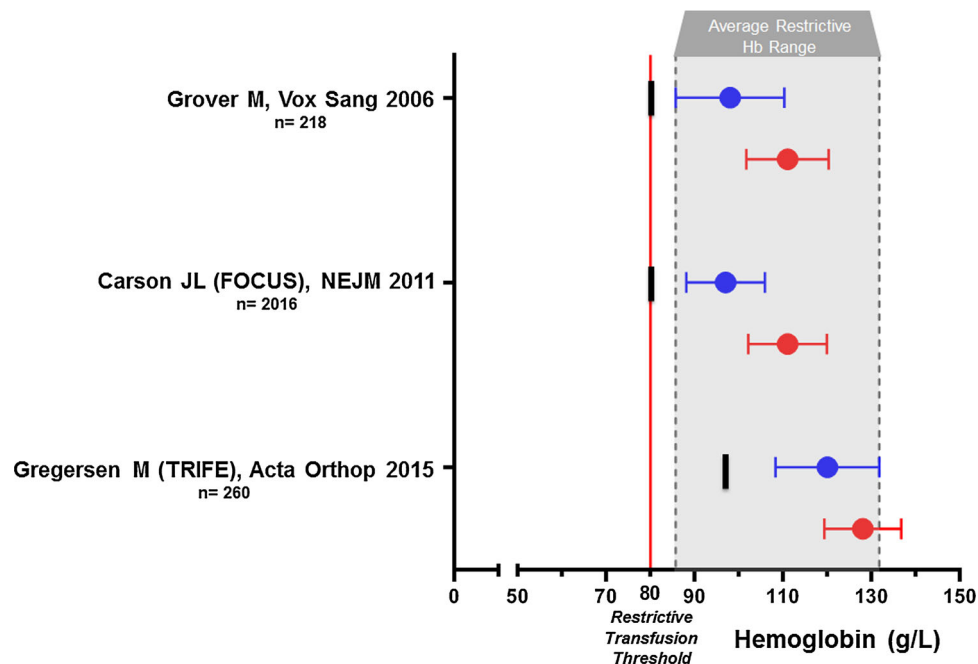
Fig. 7 Restrictive transfusion threshold and restrictive hemoglobin range (range of last measured hemoglobin before discharge in the restrictive arm) for trials assessing orthopedic surgical patients with cardiovascular risk. Black bars indicate the protocol specific restrictive transfusion trigger for each representative trial. The mean and standard deviation (SD) represents the last or pre-discharge hemoglobin level for each representative trial. Red indicates liberal treatment group, and blue indicates restrictive treatment group. The restrictive hemoglobin range (in grey) is represented by the lowest bound of the SD of the lowest restrictive treatment group, and the highest bound of the SD of the highest restrictive treatment group. The guideline recommended restrictive red blood cell transfusion threshold in orthopedic surgery patients suggests transfusion at a threshold of 80 g·L^{-1} (red line).[23] Data extracted from published trials.[67,84,85]

thresholds of 70, 75, and 80 g·L^{-1}, depending on the patient population.[23] A meta-analysis by Hovaguimian et al. in which they compared restrictive and liberal strategies in patients undergoing cardiac and non-cardiac surgery, suggested that restrictive strategies increased the risk of adverse events related to hypoxia in some patient populations.[74] In contrast to the results from the TRICS III trial, the meta-analysis by Simon et al.[89] suggested that liberal transfusion may be favourable in geriatric patients, implying that the impact of differing patient comorbidities and patient circumstances may impact outcomes associated with different treatment strategies. This data further supports individualization of transfusion strategies and, again that the transfusion thresholds may vary with clinical context.[89] Simon et al. further explain that older adults have a lower tolerance for anemia due to age-related pathophysiology, indicating that optimal patient blood management may require adaptation to individual patient settings.[90] Thus, as in other aspects of medical therapy, a one size fits all approach may not lead to the best clinical outcome; instead, a personalized approach may lead to an optimal clinical outcome.[91]

Management of anemia *vs* RBC transfusion

As preoperative anemia is one of the most consistently published risk factors for perioperative transfusion,[10,11,13] a focus on optimal treatment management of preoperative anemia to minimize the potential risk of both anemia and RBC transfusion requires ongoing attention. Ongoing clinical trials are addressing the importance of treating anemia to improve outcome in perioperative patients. These trials include the Hemoglobin Optimization to Prevent Transfusion and Adverse Events in Perioperative Patients with Iron Restricted Anemia (HOPE-Hb; ClinicalTrials.gov; NCT03528564), Preoperative Intravenous Iron to Treat Anemia in Major Surgery (PREVENTT; ClinicalTrials.gov; NCT01692418), and Intravenous Iron for Treatment of Anemia Before Cardiac Surgery (ITACS; ClinicalTrials.gov; NCT02632760), and have focused on optimal intravenous iron therapy to effectively treat anemia. In addition, two recent meta-analyses suggest that, combined treatment with iron plus erythropoiesis-stimulating agent (ESA) is safe and more effective at reducing RBC transfusion.[92,93]

Restrictive Transfusion Thresholds and Restrictive Hemoglobin Range in Cardiac Surgery
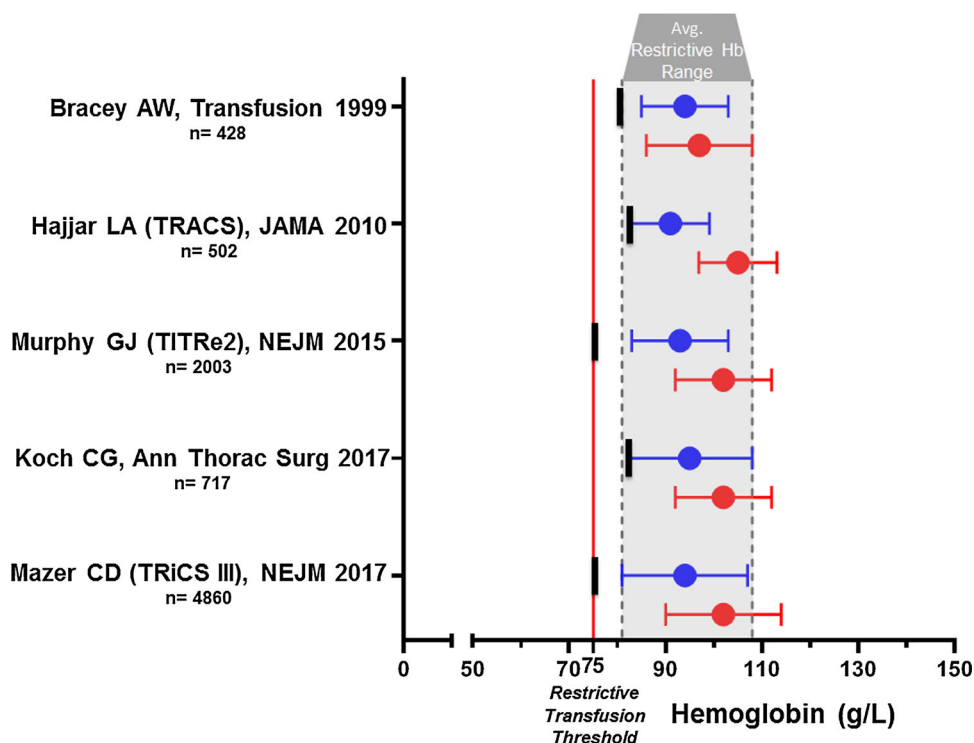

Fig. 8 Restrictive transfusion threshold and restrictive hemoglobin range (range of last measured hemoglobin before discharge in the restrictive arm) for trials assessing cardiac surgical patients. Black bars indicate the restrictive transfusion threshold for each representative trial. The mean and standard deviation (SD) represents the last or pre-discharge hemoglobin level for each representative trial. Red indicates liberal treatment group, and blue indicates restrictive treatment group. The restrictive hemoglobin range (in grey) is represented by the lowest bound of the SD of the lowest restrictive treatment group, and the highest bound of the SD of the highest restrictive treatment group. The guideline recommended restrictive red blood cell transfusion threshold in cardiac surgery patients suggests transfusion at a threshold of 75 g·L^{-1} (red line).[23] Data extracted from published trials.[66,68,86–88]

Lastly, novel oral medications that prevent HIF breakdown by inhibiting prolyl hydroxylase activity should be studied in the management of perioperative anemia.[94]

Patient blood management (PBM) programs, such as those in the United States,[95,96] Europe,[97] and Canada, including the Ontario Nurse Transfusion Coordinators (ONTraC) Program[11,13] have led to optimal management of patients while reducing adverse events associated with anemia and transfusions. These approaches have reduced unnecessary transfusion and potentially reduced the incidence of transfusion-related adverse outcomes.[96] Based on the results of these PBM programs and clinical and research recommendations presented at the 2018 Frankfurt Consensus Conference,[23] it is clear that detecting and treating preoperative anemia early before any major surgery may avoid the risks of anemia and transfusion. The causality of anemia-induced tissue hypoxia, organ injury, and subsequent mortality has not yet been established (Fig. 2). Nevertheless, management of anemia has been continually emphasized as an important and often unmet goal in medical and surgical patients.[98] Treatment algorithms have been suggested for preoperative anemia,[99] with the use of iron therapy or ESAs based on iron status. Treatment with preoperative EPO is associated with reduced perioperative blood transfusions[92,93,100] and theoretically should improve patient outcomes. Nevertheless, further research is needed to confirm optimal administration of these therapies to improve outcomes without an increase in associated adverse events (such as hypersensitivity reactions and thromboembolic events).[92]

Ongoing trials of liberal *vs* restrictive transfusion in patients with specific patient populations: traumatic brain injury and acute coronary syndromes

A number of clinical trials continue to assess the impact of liberal *vs* restrictive transfusion in different patient

populations including patients with traumatic brain injury and acute coronary syndromes.

Assessing the impact of acute anemia and cerebral hypoxia on clinical outcomes following traumatic brain injury

Two clinical trials are currently assessing the importance of the interaction between anemia, transfusions and cerebral hypoxia and other clinical outcomes following traumatic brain injury (TBI)— the HEMOglobin Transfusion Threshold in Traumatic Brain Injury OptimizatioN (HEMOTION; ClinicalTrials.gov; NCT03260478) and the Brain Oxygen Optimization in Severe TBI Phase 3 study (BOOST III; ClinicalTrials.gov; NCT03754114). From published studies, we know that systemic hypoxia/hypoxemia is a significant risk factor for secondary brain injury following TBI.[101] With the introduction of direct brain tissue PO_2 measurements using implanted Clark-type electrodes, low brain PO_2 has been identified to be a prognostic indicator of poor outcomes including worsened brain injury and mortality.[102,103] Furthermore, an interaction was observed between low Hb and low brain PO_2 (< 20 mmHg) such that the combination of these two clinical indicators was associated with an unfavourable outcome (defined as a Glasgow Comma Scale 1–3 at 30 days; OR, 6.24; 95% CI, 1.61 to 24.22; $P = 0.008$).[104] An experimental study has supported a causal role for anemia-induced brain tissue hypoxia as a mediator of increased brain injury by showing that acute anemia reduces brain PO_2, and that very small decreases in brain PO_2 are associated with up to three-fold increases in cerebral infarction volume.[105] Additionally, the type of resuscitation fluid (including blood) has a significant impact on the recovery of brain PO_2 and on brain electrical activity in another experimental study.[106] Nevertheless, whether active treatments to increase brain tissue PO_2, including correction of anemia, can significantly improve outcomes in patients with TBI remains to be determined. A treatment protocol for TBI based on monitoring and maintaining adequate brain PO_2 has been suggested.[107] Okonkwo et al. have provided data in support of the hypothesis that this treatment protocol, designed to improve brain perfusion and real-time brain tissue PO_2, may increase functional outcomes after TBI (BOOST II).[108] This hypothesis is being more completely assessed in a multi-national phase III clinical trial (BOOST III).

Retrospective and early randomized prospective studies have assessed the risk-benefit of liberal transfusion strategies in patients who have suffered a TBI.[109,110] Despite the evidence suggesting the harmful effects of anemia and low brain PO_2 following TBI, a clear benefit from liberal transfusion is not supported by all studies.[109,110] As a consequence, some authors are calling for more rigorous non-inferiority RCTs to evaluate liberal vs restrictive transfusion practices following TBI.[111] Ongoing trials, such as HEMOTION, have sought to fill a similar knowledge gap by examining the superiority of liberal transfusion strategies (trigger ≤ 100 g·L^{-1}) vs restrictive strategies (trigger ≤ 70 g·L^{-1}) with respect to neurologic functional outcomes. Unfortunately, this study will also simply assess the superiority of one arbitrary transfusion trigger vs another arbitrary trigger. There is also a need for studies which address individualizing transfusion based on clinical and/or physiologic parameters. As an alternative to transfusion, some groups have evaluated administering ESAs to improve outcomes in TBI.[109] Therefore, although the decrease in brain PO_2 due to anemia has a negative impact on outcomes in TBI patients, the advantage of treating this low PO_2 value, through a number of treatments including RBC transfusion, remains to be shown.

Assessing the impact of anemia on acute coronary syndrome

One of the ongoing large RCTs evaluating the effect of anemia and transfusion on outcomes in acute coronary syndrome is the Myocardial Ischemia and Transfusion (MINT) trial (NCT02981407). Hébert et al. suggested that restrictive transfusion strategies might not be safe in patients with acute MIs or unstable angina.[78] Carson et al. identified a lack of high quality RCTs to guide transfusion practices in patients with ACS. In a pilot trial, Carson et al. found that liberal transfusion strategies showed a trend of superiority compared with restrictive strategies, with regards to major cardiac events and deaths.[80] As a result, they are currently conducting the Phase III MINT trial (NCT02981407), with the purpose of filling this knowledge gap.

Conclusions

In summary, based on the evidence provided by high-quality RCTs, associated meta-analyses, and derived guidelines, the determination of an appropriate Hb threshold for RBC transfusion may vary depending on important patient factors and clinical circumstances. The concept of a one size fits all approach to anemia and transfusion based purely on Hb levels should be rigorously re-evaluated.

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