Anemia: Perioperative Risk and Treatment Opportunity

Gregory M. T. Hare, M.D., Ph.D., C. David Mazer, M.D.

Current estimates suggest that over 1 billion humans suffer from anemia worldwide. Anemia remains one of the top causes of years lived with disability globally.[1] Anemia is also prevalent in patients with critical illness[2] and those presenting for surgical care.[3] The strong association between anemia and perioperative morbidity and mortality has captured the attention of anesthesiologists.[3–14] Understanding this risk has energized clinician and investigators to pursue the goal of defining the pathophysiology of this heterogeneous and complex disorder and formulating effective treatment strategies.[15] By understanding the potential mechanism(s) of injury associated with anemia, we may enhance implementation of available effective strategies to treat anemia and also develop novel treatment strategies. These approaches may reduce the incidence of adverse outcomes associated with anemia.

Defining the Risk of Anemia in the Perioperative Setting

The World Health Organization (Geneva, Switzerland) has defined anemia as a hemoglobin concentration less than 13 g · dl^{-1} in men and 12 g · dl^{-1} in women.[14] The incidence of erythrocyte transfusion has been demonstrated to increase below a preoperative hemoglobin concentration of 13 g · dl^{-1}.[16] In a recent review by Warner *et al.*, the authors suggest utilizing a definition of a hemoglobin concentration less than 13 g · dl^{-1} for both sexes[15] given that anemia increases the risk of erythrocyte transfusion and associated adverse outcomes in perioperative patients.[14,16,17]

In an attempt to better classify the risk of anemia exposure, clinical studies have focused on the impact of (1) preoperative anemia (chronic or preexisting anemia),[3–6] (2) acute intraoperative anemia[7–10,18,19] (usually associated with acute blood loss and fluid resuscitation), and (3) postoperative anemia,[11–13] which is strongly influenced by the combined impact of preoperative and intraoperative anemia. Studies have also assessed the risk of anemia in patients undergoing both noncardiac and cardiac surgery. Evidence supports that the relative percent change in hemoglobin concentration, or "delta hemoglobin concentration," is also an important predictor of adverse outcomes.[20,21] Finally, physiologic adaptations to chronic anemia, including an increase in 2,3-diphosphoglycerate, among other mechanisms, may be protective, as the risk of mortality associated with chronic anemia appears to be lower than for patients with acute anemia.[14,22]

Understanding the mechanism(s) of organ injury and death associated with anemia is central to developing, and applying, effective treatments in an attempt to prevent these adverse outcomes. For the purposes of this review, we will evaluate the evidence assessing whether anemia, of any timing or etiology, presents an increased risk for adverse outcomes. Evidence that a common mechanism, such as limited oxygen delivery to tissue (*i.e.*, tissue hypoxia), may contribute to adverse outcomes in anemic patients has been supported by data derived from models of experimental anemia.[23–27] These studies support the hypothesis that anemia-induced tissue hypoxia may contribute to the pathophysiology associated with clinical anemia (fig. 1).[28] Identifying such a unifying mechanism would help to characterize the overlapping risk that appears to be associated with all types of anemia. This approach includes the assessment that anemia may represent an independent causal risk factor for organ injury and mortality, but does not exclude the possibility that anemia may also be a "biomarker" of severity of patient comorbidity, which could also influence patient outcome.[14]

Perioperative Anemia Is Prevalent and Is Associated with Vital Organ Injury

Data from large retrospective databases and prospective cohort studies demonstrate that about 30% of patients presenting for cardiac and noncardiac surgery are anemic.[3,4,6,17,29] In these studies, both "*chronic*" preoperative and "*acute*" intraoperative anemia have been associated with increased organ injury and mortality. The presence of chronic preoperative and acute intraoperative anemia is a strong predictor of postoperative mortality after both cardiac[4,5,8,29] and noncardiac surgery.[3,6,12,13,17] When considering the mechanism of organ injury, the impact of acute anemic-tissue hypoxia (cellular energetic failure) and the associated responses including renal tissue hypoxia, increased cardiac output, and myocardial

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue. 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).

Submitted for publication February 4, 2021. Accepted for publication June 1, 2021. Published online first on July 1, 2021. From the Department of Anesthesia and the Keenan Research Centre for Biomedical Science in the Li Ka Shing Knowledge Institute, St. Michael's Hospital (G.M.T.H., C.D.M.), Department of Physiology (G.M.T.H., C.D.M.), and Institute of Medical Science (C.D.M.), Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Ontario, Canada.

 Anesthesiology 2021; 135:520–30. DOI: 10.1097/ALN.0000000000003870

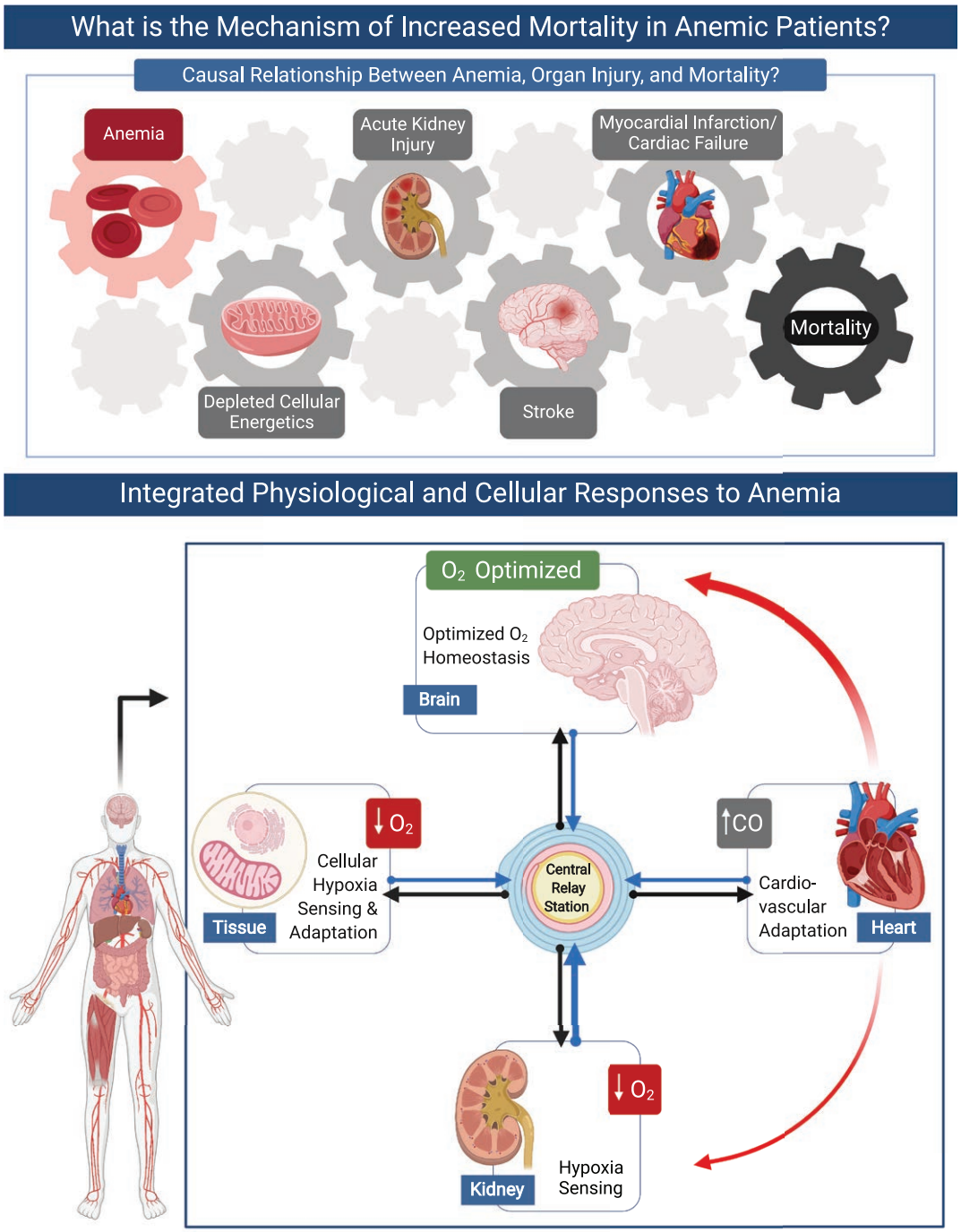

Fig. 1. *Top*: Evidence supports an association between the degree of anemia and organ injury, including depleted cellular energetics, kidney injury, stroke, and myocardial injury/cardiac failure. The interlinking cogs indicate that causality between anemia, organ injury, and mortality has not been clearly established, and that differing connections between morbidities may occur. *Bottom*: This schematic figure depicts the integrated physiologic responses to acute anemia, including hypoxia sensing at the tissue level. The integrated physiologic response to anemia-induced tissue hypoxia supports that afferent signals (*blue arrows*) are received from the peripheral tissues, including the kidneys and other organs, and are sent to a central relay station (central nervous system). Central processing results in coordinated afferent signals (*black arrows*) that contribute to graded responses, including an increase in cardiac output (CO) and increased regional blood flow to organs of high metabolic need, including the brain (*upper red arrow*). Blood flow to other organs such as the kidney may have a limited blood flow response, possibly contributing to the kidney's ability to sense changes in blood oxygen content during anemia. At the cellular levels, hypoxic regulatory mechanisms including hypoxia-inducible factor α in all cells contribute to cellular adaptation to acute anemic hypoxia.

work, and the increase in cerebral blood flow associated with anemia may all contribute to optimized organ perfusion but also may contribute to the observed phenotypes of organ injury and increased mortality (fig. 1).

Acute Kidney Injury

Analyses of large retrospective databases have identified that preoperative anemia is associated with an increased risk of acute kidney injury in patients undergoing cardiac and noncardiac surgery.[4,5,17] Acute hemodilution on cardiopulmonary bypass has also been associated with acute kidney injury and dialysis dependence after surgery in a manner that is proportional to the degree of acute hemodilution.[8,18]

Stroke

Preoperative and acute intraoperative anemia have been associated with stroke in a manner that is proportional to the degree of preoperative anemia and the nadir hemoglobin concentration that occurred during surgery.[4,5,11,19]

Myocardial Injury/Infarction

Analysis of the impact of acute intraoperative anemia has demonstrated an increased risk of myocardial infarction with decreasing hemoglobin levels.[10,22] More recent retrospective analyses of data from large prospective randomized controlled trials and cohort studies have identified that intraoperative and postoperative anemia are both associated with elevated troponin levels, myocardial injury. and mortality after cardiac[5,8] and noncardiac surgery.[6,10,12]

Defining the Association between Anemia and Adverse Outcomes in Large Retrospective Studies

Analysis of large clinical studies provides some insights into the magnitude of risk associated with anemia. A retrospective analysis of 227,425 patients undergoing noncardiac surgery, based on data from the American College of Surgeons (Chicago, Illinois) National Surgical Quality Improvement Program database, demonstrated that 69,229 (approximately 30%) of these patients were anemic.[17] Patients with anemia had an increased adjusted odds ratio for mortality (odds ratio, 1.42 [95% CI, 1.31 to 1.54]), cardiac injury (odds ratio, 1.45 [95% CI, 1.29 to 1.65]), respiratory dysfunction (odds ratio, 1.33 [95% CI, 1.26 to 1.41]), and renal injury (odds ratio, 1.37 [95% CI, 1.23 to 1.53]).[17] Results from the International Surgical Outcomes Study database demonstrated that 11,675 (approximately 30%) of 38,770 patients had anemia. Patients diagnosed with moderate anemia (8.0 to 10.9 $g \cdot dl^{-1}$) had an increased risk of in hospital mortality (odds ratio, 2.70 [95% CI, 1.88 to 3.87]) and myocardial infarction (odds ratio, 1.58 [95% CI, 1.00 to 2.49]).[3] Anemia also increased risk of mortality and morbidity after cardiac surgery.[4,5,29] Klein *et al.* described an analysis of 19,033 patients undergoing cardiac surgery of whom 5,895 (31%) had a diagnosis of anemia. Within this cohort, preoperative anemia was associated with increased mortality (odds ratio, 1.42 [95% CI, 1.18 to 1.71]).[29] Karkouti *et al.* published similar data indicating that about 26% of 3,500 patients with anemia experienced an increased risk of a composite outcome of in-hospital death, stroke, and acute kidney injury (odds ratio, 1.8 [95% CI, 1.2 to 2.7]).[4] Studies that stratify the degree of anemia demonstrate that the magnitude of the risk tends to progress with the severity of anemia from mild to moderate and severe.[3–5,17]

Severity of Anemia and Adverse Outcomes

The relationship between the degree of acute anemia and risk of adverse outcomes has been clearly described in (1) patients undergoing noncardiac surgery who refuse blood transfusion[7,9,14,22,30,31] and (2) anemic patients who experience acute hemodilution on cardiopulmonary bypass.[4,5] For patients who refuse erythrocyte transfusion,[22,30,31] the severity of acute anemia predicts mortality such that each 1 $g \cdot dl^{-1}$ decrease in hemoglobin concentration predicts an increased risk of mortality (odds ratio, 1.55 [95% CI, 1.25 to 1.91]).[7,22] The estimated hemoglobin concentration at which 50% mortality occurs is near 3 $g \cdot dl^{-1}$, coincident with the hemoglobin concentration below which oxygen metabolism becomes supply-dependent.[31] Time to death is accelerated in patients who experience critically low hemoglobin levels,[7] and 100% mortality is predicted for patients with extremely low hemoglobin levels.[7,9,14,31]

In patients with severe acute anemia, treatment with hemoglobin-based oxygen carriers has been attempted to offset the high risk of mortality at very low hemoglobin levels.[9,31] Under these conditions, treatment with hemoglobin-based oxygen carriers may reduce the incidence of mortality (hazard ratio, 0.42 [95% CI, 0.25 to 0.86]).[9,31] However, these agents have not received regulatory approval in North America, and the potential benefits of utilizing hemoglobin-based oxygen carriers to treat severe life-threatening anemia must be weighed against data from clinical trials suggesting that some hemoglobin-based oxygen carriers may increase the risk of cardiac injury and mortality in less severely anemic patients.[32]

Further evidence supporting a possible causal link between anemia, organ injury, and mortality is provided by analyses of the impact of acute hemodilutional anemia in surgical patients undergoing acute hemodilution during cardiopulmonary bypass. In patients undergoing cardiac surgery, the lowest hemoglobin concentration or hematocrit on bypass has been associated acute kidney injury,[8,18] myocardial infarction,[8] and stroke.[19] In each case, the incidence of injury is proportional to the degree of acute anemia. Thus, a relationship has been defined between the degree of acute anemia, acute kidney injury, stroke and myocardial injury, and mortality, raising the possibility that severe acute anemia limits tissue oxygen delivery and results in organ injury and mortality (fig. 1).

The Risk of Anemia and Erythrocyte Transfusion Are Closely Associated

Preoperative and intraoperative anemia are among the strongest risk factors for intraoperative transfusion.[16,29,33] Thus, the risks of anemia and erythrocyte transfusion are tightly linked or "intertwined."[14,34] Since both anemia and transfusion have been associated with adverse outcomes, it remains difficult to isolate the attributable risk from each exposure.[34] This combined risk strongly emphasizes the potential benefit of effective patient blood management and treatment of preoperative anemia to avoid the potential risk of both anemia and transfusion.[14,15,35]

The Potential Roles of Hypoxia-inducible Factor to Maintain Oxygen Homeostasis and Organism Survival

Experimental studies that have investigated the physiologic adaptation of mammals to acute anemia have consistently demonstrated that the oxygen-sensing mechanisms involved are extremely sensitive, complex, and redundant, emphasizing the importance of maintaining adequate oxygen delivery to tissue to maintain survival.[14,24,36,37] These mechanisms are capable of detecting early changes in arterial oxygen content (Cao_2) and then amplifying integrated adaptive responses in a manner that is proportional to the severity reduced Cao_2.[23,25,26,38,39] This assumes that effective mechanisms exist to (1) sense changes in Cao_2, (2) generate afferent signals to inform central and/or peripheral processing centers that tissue hypoxia is occurring, and (3) generate efferent responses to activate cardiovascular responses that increase cardiac output, vital organ blood flow, and tissue oxygen delivery to preserve vital organ perfusion, tissue oxygen homeostasis, and cellular function (fig. 1).[24,26,27,38,39]

One of the primary cellular responses to inadequate tissue oxygen delivery is to enhance or activate adaptive hypoxic cellular mechanism(s) including those derived from hypoxia-inducible factor, the master genetic regulator of hypoxic cellular responses.[37] The importance of oxygen sensing at the cellular level is supported by the ubiquitous presence of hypoxia-inducible factor, and other oxygen sensing mechanisms (mitochondria), that are present in every cell in the human body (fig. 1).[36,37] The importance of hypoxia-inducible factor in maintaining organism homeostasis and survival during acute anemia is demonstrated by the finding that when this system is disrupted, an increase in anemia-induced mortality is observed.[26] These translational studies support the hypothesis that hypoxic cellular responses are initially adaptive and indicate the presence of anemia-induced tissue hypoxia. Further clinical studies are required to determine if these "hypoxic biomarkers" can be measured in patients and utilized to predict adverse outcomes, and direct treatment to improve patient care.[28]

Treatments of Anemia to Improve Patient Outcomes: The Role of Patient Blood Management

The important role of patient blood management as a means of avoiding the negative impact of both anemia and erythrocyte transfusion has been strongly emphasized.[14–16] Prospectively collected data have demonstrated that integrated blood management programs are associated with reduced erythrocyte transfusion and improved patient outcomes.[15,16,35] Published reviews have clearly outlined the diagnostic criteria for iron deficiency and iron restrictive anemia as well as the specific algorithms for treatment, including oral and iv iron and erythroid stimulating agents (table 1).[15,35,40] A recently published network meta-analysis identified that patient blood management resulted in reduction in risk of erythrocyte transfusion (risk ratio, 0.60 [95% CI, 0.57 to 0.63; $I^2 = 77\%$]) and favored shorter intensive care and hospital length of stay but did not influence mortality or other adverse outcomes.[35] These findings support the approach to avoid "anemia neglect" and to apply appropriate resources and initiatives to treat anemia preoperatively, and not to rely entirely on erythrocyte transfusion as a default treatment.[15] The approach to optimal patient blood management requires an appreciation of the potential harm associated with both anemia and erythrocyte transfusion[14,34] as well as allocation of adequate resources to enable effective treatments. To successfully achieve optimal patient blood management practices, clinicians and investigators have assessed different approaches, and timelines, to treating preoperative anemia (fig. 2; table 1).

The Use of IV Iron to Treat Preoperative Anemia

While oral iron therapy has long been the mainstay of treatment of iron-deficient anemia, the duration of therapy, low bioavailability, and lack of tolerance to oral iron often make this approach inadequate for rapid preoperative treatment of iron-deficient anemia. This has promoted the adoption of intravenous iron as a means of more rapidly replenishing iron stores and improving hemoglobin levels. A recent trial assessing efficacy of iv *versus* oral iron therapy in blood donors demonstrated that a single dose of iv iron was more effective than oral iron at increasing iron stores as reflected by ferritin levels (median, 105 [interquartile range, 75 to 145] *vs.* 25 [17 to 34] ng/ml).[47] In support of this finding, a systematic review has reported evidence that supports that iv iron was more effective than oral iron at reducing erythrocyte transfusion in surgical patients.[48] The recently published Preoperative Intravenous Iron to Treat Anemia Before Major Abdominal Surgery (PREVENTT) trial assessed the impact of iv iron on anemic patients after abdominal surgery.[49] While no difference in erythrocyte transfusion was observed, patients in the treatment arm had higher postoperative hemoglobin levels (at 8 weeks and 6 months) and had significantly fewer readmissions to the hospital (6 months).[49,50] Limitations of this trial

Table 1. Diagnosis and Treatment of Anemia

General Treatment Suggestions Based on Warner *et al.*, 2020[15] and Goodnough and Shander, 2012[40]	Iron Deficiency without Anemia	Iron Deficiency Anemia	Iron-restricted Anemia (Inflammation)	Mixed Anemia
For diagnoses of anemia	Consider potential sources of blood loss: gastrointestinal, gynecological, other; malabsorption; hemoglobinopathy; diseases of bone marrow, renal failure, other nutritional deficiencies such as B_{12} and folate, and initiate appropriate medical referral.			
Laboratory tests (with approximate normal values in parentheses)				
(1) Hb concentration (Hb > 12 female, or 13 male, g/dl)	Normal	↓	↓	↓
(2) Ferritin (20–200 μg/l)	↓	↓	↑	Normal or ↑
(3) Serum iron (10–30, μM/l)	↓	↓	Normal or ↓	↓
(4) Transferrin saturation (20–50%)	↓	↓	Normal or ↓	↓
(5) Reticulocyte Hb content (30–35 pg)	↓	↓	Normal or ↓	Normal or ↓
(6) Total iron binding capacity (240–450 μg/dl)	↑	↑	↓	↔
(7) Hepcidin (not readily available)	↓	↓	↑	Normal or ↑
Iron therapy				
(1) Consider oral iron therapy	Yes	Yes	Yes	Yes
(2) Consider intravenous iron therapy (if oral therapy not tolerated/effective, or impending urgent surgery)	Yes	Yes	Yes	Yes
Erythrocyte-stimulating agent				
Consider if iron therapy alone is ineffective in raising Hb (anemia not responsive) and if increasing the Hb level remains an important treatment goal	No	Yes	Yes	Yes

Hb, hemoglobin.

include the lack of diagnosis of iron deficiency (anemia etiology) and the relatively short duration between treatment and surgery in patients treated with iv iron, which may have negatively impacted the efficacy of iv iron therapy.[50] The synthesis of these data and studies suggests that iv iron may be a more effective means of restoring iron levels and improving patient outcomes, but that by itself, iv iron preoperatively may not readily reduce erythrocyte transfusion.

What Is the Evidence for Combined Erythropoiesis-stimulating Agents and Iron?

The efficacy of erythropoiesis-stimulating agents and iron *versus* iron alone have been assessed in two recent meta-analyses.[51,52] The data from these analyses support that addition of an erythropoiesis-stimulating agent to iron (oral or iv) is superior to iron therapy alone with respect to erythrocyte transfusion avoidance. Specifically, treatment with combined erythropoiesis-stimulating agent and iron therapy for patients undergoing orthopedic and cardiac surgical procedures resulted in a reduction in the risk of erythrocyte transfusion relative to iron therapy alone (odds ratio, 0.49 [95% CI, 0.32 to 0.76] and 0.51 [0.32 to 0.79], respectively).[52] These positive outcomes were not associated with an increased in thrombotic complications including deep vein thrombosis or pulmonary embolism, supporting that these approaches can be safe.[51,52] This clinical data must be balanced with the potential risks of erythropoiesis-stimulating agent therapy as outlined in the revised black box warning from the U.S. Food and Drug Administration (Silver Spring, Maryland), which warns that research has found a higher risk of death, heart disease, and stroke in those who took erythropoiesis-stimulating agents.[53]

Can Treatment at the Time of Surgery Reduce Erythrocyte Transfusion?

Given the challenges of arranging preoperative assessment and treatment and the frequent need for urgent surgery, many studies have assessed the impact of acute treatment of anemia at the time of admission for surgery. Support for a combined pharmaceutical approach including an erythropoiesis-stimulating agent plus nutritional supplementation (iron, B_{12}, folate) is provided by the data from a recent randomized controlled trial in patients undergoing cardiac surgery.[54] The authors of this study demonstrate that acute therapy near the time of surgery reduced the incidence of erythrocyte transfusion in this patient population at high risk for transfusion (erythrocyte transfusion, median, 0 [interquartile range, 0 to 2] *vs.* 1 [interquartile range, 0 to 3] units), and treated patients had a higher reticulocyte count and reticulocyte hemoglobin content at 7 days.[54] A subanalysis of available studies comparing the impact of anemia treatment just before the time of surgery, which include one dose of an erythropoiesis-stimulating agent, suggests that this approach may reduce erythrocyte transfusion (relative risk, 0.80 [95% CI, 0.57 to 1.11]; $I^2 = 80\%$; $P = 0.18$) and increased postoperative hemoglobin levels (mean difference, 0.53 [95% CI, –0.05 to 1.12] g · dl^{-1}; $I^2 = 95\%$; $P = 0.08$). The overall small samples sizes and high degree of study heterogeneity suggest that additional adequately powered trials are required to fully assess the efficacy, and safety, of this approach (fig. 2).

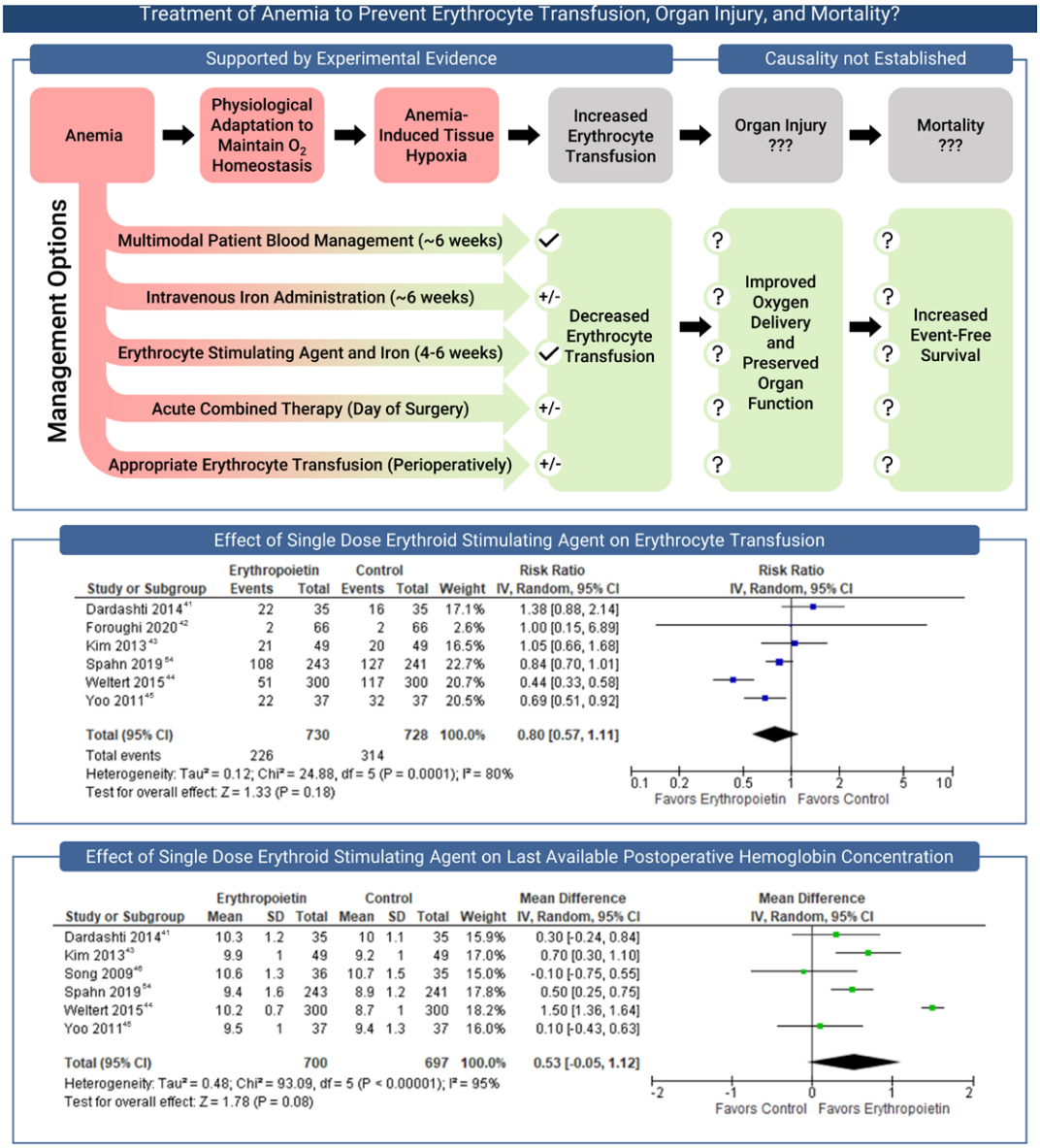

Fig. 2. *Upper*. The impacts of anemia on adaptive cardiovascular and cellular changes and erythrocyte transfusion have been supported by evidence. However, these impacts have not clearly been linked to organ injury or mortality. The transitional *red to green arrows* depict different established management options to treat perioperative anemia, including the estimated time required for treatment. Some of these treatments, including multimodal patient blood management and combined iron and erythroid-stimulating agents, have been shown to reduce erythrocyte transfusion (*check marks*), while other approaches may or may not reduce (*+/–*), erythrocyte transfusion. None of these treatments have been demonstrated to reduce organ injury and/or mortality in larger prospective trials. *Lower*. An analysis of randomized trials that initiate treatment of anemia near the time of surgery demonstrate a trend to reducing erythrocyte transfusion (risk ratio, 0.80 [95% CI, 0.57 to 1.11]; $P = 0.18$) and increasing postoperative hemoglobin level (g · dl^{-1}; mean difference, 0.53 [95% CI, 0.05 to 1.12]; $P = 0.08$; see full methods and references in Supplemental Digital Content, http://links.lww.com/ALN/C644). The small sample sizes and large degrees of heterogeneity (I^2) between these studies indicate that additional large randomized trials are required to more clearly establish efficacy and safety.

What Is the Role for Appropriate Erythrocyte Transfusion?

While evidence of adverse events associated with erythrocyte transfusion supports continued efforts to promote patient blood management programs, the knowledge that severe acute anemia will lead to increased mortality[7,30] requires us to carefully balance the risks of anemia with the risks of transfusion.[14] With a growing number of trials assessing restrictive

versus liberal approaches to erythrocyte transfusion, a frequent analysis or recommendation remains that a restrictive transfusion strategy is noninferior to a more liberal strategy in terms of mortality and major morbidity.[55,56] However, a closer look at this overall approach is required as subanalysis of these studies supports the hypothesis that different transfusion strategies may be appropriate for patient populations who undergo different surgical procedures.[57] Indeed, recent guidelines for perioperative erythrocyte transfusion have supported the approach that different patient populations have evidence for different erythrocyte transfusion thresholds.[58] Other hypothesis generating data in support of defining erythrocyte transfusion thresholds in specific patient populations is derived from the Transfusion Requirements in Cardiac Surgery III (TRICS-III) study, the largest clinical trial assessing liberal *versus* restrictive transfusion in cardiac surgery.[59] With respect to the primary composite outcomes of death, myocardial infarction, stroke, and new-onset renal failure requiring dialysis at 6 months after surgery, there was strong suggestive evidence for effect modification by age, where a restrictive strategy was favored in patients 75 yr and older (n = 2,327; odds ratio, 0.77 [95% CI, 0.62 to 0.96]), and a liberal strategy was favored in patients younger than 75 yr (n = 2,337; odds ratio, 1.32 [95% CI, 1.07 to 1.64]; $P_{\text{interaction}} = 0.001$).[59] A study testing the hypothesis that liberal transfusion therapy may be superior to a restrictive strategy in younger patients undergoing cardiac surgery is currently underway (Transfusion Requirements in Younger Patients Undergoing Cardiac Surgery [TRICS-IV], NCT04754022).

What Novel Treatments of Anemia Are on the Horizon

Basic science research has demonstrated that anemia activates a number of profound cellular and physiologic adaptations including hypoxic cellular responses, such as hypoxia-inducible factor.[25,26,39] Hypoxia-inducible factor was discovered as the promotor of hypoxia-induced erythropoietin transcription.[37] As such, pharmacologically augmenting the hypoxia-inducible factor response in anemic patients may act to correct anemia and protect against hypoxic cellular injury.[26] This potential has led to the development of a number of pharmaceuticals targeting the inhibition of the enzyme hypoxia-inducible factor prolyl-hydroxylases, which are primarily responsible for initiating the degradation of hypoxia-inducible factor α. Inhibiting these enzymes serves to augmenting the hypoxia-inducible factor response, including promotion of erythrogenesis and inhibition of hepcidin, a molecule that limits iron transport.[60,61] A recent network meta-analysis assessed the efficacy of a number of oral hypoxia-inducible factor prolyl-hydroxylase inhibitors to determine if they are as effective as erythropoiesis-stimulating agent therapies at treating anemia.[62] Two of the largest prospective trials reported the efficacy of roxadustat *versus* placebo or recombinant erythropoietin, with respect to increasing hemoglobin concentration in anemic patients with renal dysfunction.[60,61] They observe that roxadustat increased hemoglobin levels (erythropoiesis) and reduced hepcidin (leads to increased iron transport) in a manner that was noninferior to recombinant erythropoietin.[60] The incidence of serious adverse events, 29 (14.2%) *versus* 10 (10%), suggests the need for future trials to assess safety and their potential role in the perioperative setting.[60]

In summary, perioperative anemia is associated with adverse outcomes by complex and incompletely understood mechanisms. At severe levels of anemia, insufficient tissue oxygen delivery likely contributes to organ injury and increased mortality. Clinical and experimental studies have defined the strong adaptive hypoxic cellular responses to acute anemia, which in part explain the intrinsic mechanism(s) of adaptation to anemia, as well as potential mechanisms(s) of anemia-induced morbidity and mortality. Evidence of morbidity and mortality associated with all levels of anemia suggest that ongoing adequately powered clinical trials are needed to define treatment strategies that both improve anemia and prevent adverse clinical outcomes in anemic patients undergoing cardiac and noncardiac surgery.

Acknowledgments

The authors would like to acknowledge Richard B. Weiskopf, M.D., Professor Emeritus, University of California, San Francisco (San Francisco, California) for his related research and thoughtful review of an earlier version of this manuscript. All figures were created by Iryna Savinova, M.Sc., Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada. Fig. 1 was designed using BioRender.com (Toronto, Ontario, Canada). The forest plot analysis assessing the impact of a single dose of erythropoiesis-stimulating agent was performed by Nikhil Mistry, M.Sc. (Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada).

Research Support

Drs. Hare and Mazer were supported by University of Toronto (Toronto, Ontario, Canada) Merit Awards.

Competing Interests

Dr. Hare has received honoraria support from Pfizer (Kirkland, Quebec, Canada) and Johnson & Johnson (Markham, Ontario, Canada). Dr. Mazer has received advisory board honoraria from Amgen (Mississauga, Ontario, Canada), AstraZeneca (Mississauga, Ontario, Canada), Boehringer Ingelheim (Burlington, Ontario, Canada), and Octapharma (Toronto, Ontario, Canada).

Correspondence

Address correspondence to Dr. Hare: Department of Anesthesia, St. Michael's Hospital, 30 Bond Street, Toronto,

Ontario M5B 1W8, Canada. greg.hare@unityhealth.to.

References

1. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW: Iron deficiency. Lancet 2021; 397:233–48
2. Warner MA, Hanson AC, Frank RD, Schulte PJ, Go RS, Storlie CB, Kor DJ: Prevalence of and recovery from anemia following hospitalization for critical illness among adults. JAMA Netw Open 2020; 3:e2017843
3. Fowler AJ, Ahmad T, Abbott TEF, Torrance HD, Wouters PF, De Hert S, Lobo SM, Rasmussen LS, Della Rocca G, Beattie WS, Wijeysundera DN, Pearse RM; International Surgical Outcomes Study Group: Association of preoperative anaemia with postoperative morbidity and mortality: An observational cohort study in low-, middle-, and high-income countries. Br J Anaesth 2018; 121:1227–35
4. Karkouti K, Wijeysundera DN, Beattie WS; Reducing Bleeding in Cardiac Surgery (RBC) Investigators: Risk associated with preoperative anemia in cardiac surgery: A multicenter cohort study. Circulation 2008; 117:478–84
5. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehnle P, Mangano DT; Investigators of the Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation: Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation 2007; 116:471–9
6. Beattie WS, Karkouti K, Wijeysundera DN, Tait G: Risk associated with preoperative anemia in noncardiac surgery: A single-center cohort study. Anesthesiology 2009; 110:574–81
7. Guinn NR, Cooter ML, Weiskopf RB: Lower hemoglobin concentration decreases time to death in severely anemic patients for whom blood transfusion is not an option. J Trauma Acute Care Surg 2020; 88:803–8
8. Loor G, Li L, Sabik JF III, Rajeswaran J, Blackstone EH, Koch CG: Nadir hematocrit during cardiopulmonary bypass: End-organ dysfunction and mortality. J Thorac Cardiovasc Surg 2012; 144:654–662.e4
9. Weiskopf RB, Glassberg E, Guinn NR, James MFM, Ness PM, Pusateri AE: The need for an artificial oxygen carrier for disasters and pandemics, including COVID-19. Transfusion 2020; 60:3039–45
10. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G, Mitsakakis N, Hare GM: Acute surgical anemia influences the cardioprotective effects of beta-blockade: A single-center, propensity-matched cohort study. Anesthesiology 2010; 112:25–33
11. Ashes C, Judelman S, Wijeysundera DN, Tait G, Mazer CD, Hare GM, Beattie WS: Selective β1-antagonism with bisoprolol is associated with fewer postoperative strokes than atenolol or metoprolol: A single-center cohort study of 44,092 consecutive patients. Anesthesiology 2013; 119:777–87
12. Turan A, Cohen B, Rivas E, Liu L, Pu X, Maheshwari K, Farag E, Onal O, Wang J, Ruetzler K, Devereaux PJ, Sessler DI: Association between postoperative haemoglobin and myocardial injury after noncardiac surgery: A retrospective cohort analysis. Br J Anaesth 2021; 126:94–101
13. Turan A, Rivas E, Devereaux PJ, Bravo M, Mao G, Cohen B, Maheshwari K, Pu X, Ruetzler K, Li K, Sessler DI: Association between postoperative haemoglobin concentrations and composite of non-fatal myocardial infarction and all-cause mortality in noncardiac surgical patients: Post hoc analysis of the POISE-2 trial. Br J Anaesth 2021; 126:87–93
14. Shander A, Javidroozi M, Ozawa S, Hare GM: What is really dangerous: Anaemia or transfusion? Br J Anaesth 2011; 107(suppl 1):i41–59
15. Warner MA, Shore-Lesserson L, Shander A, Patel SY, Perelman SI, Guinn NR: Perioperative anemia: Prevention, diagnosis, and management throughout the spectrum of perioperative care. Anesth Analg 2020; 130:1364–80
16. Hare GM, Freedman J, David Mazer C: Review article: Risks of anemia and related management strategies: Can perioperative blood management improve patient safety? Can J Anaesth 2013; 60:168–75
17. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, Khreiss M, Dahdaleh FS, Khavandi K, Sfeir PM, Soweid A, Hoballah JJ, Taher AT, Jamali FR: Preoperative anaemia and postoperative outcomes in non-cardiac surgery: A retrospective cohort study. Lancet 2011; 378:1396–407
18. Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE: Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg 2005; 129:391–400
19. Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeysundera D, Ivanov J, Karski J: Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. Ann Thorac Surg 2005; 80:1381–7
20. Hogervorst E, Rosseel P, van der Bom J, Bentala M, Brand A, van der Meer N, van de Watering L: Tolerance of intraoperative hemoglobin decrease during cardiac surgery. Transfusion 2014; 54(10 pt 2):2696–704
21. Spolverato G, Kim Y, Ejaz A, Frank SM, Pawlik TM: Effect of relative decrease in blood hemoglobin concentrations on postoperative morbidity in patients who

undergo major gastrointestinal surgery. JAMA Surg 2015; 150:949–56
22. Guinn NR, Cooter ML, Villalpando C, Weiskopf RB: Severe anemia associated with increased risk of death and myocardial ischemia in patients declining blood transfusion. Transfusion 2018; 58:2290–6
23. Abrahamson JR, Read A, Chin K, Mistry N, Joo H, Desjardins JF, Liu E, Thai K, Wilson DF, Vinogradov SA, Maynes JT, Gilbert RE, Connelly KA, Baker AJ, Mazer CD, Hare GMT: Renal tissue Po(2) sensing during acute hemodilution is dependent on the diluent. Am J Physiol 2020; 318:R799–R812
24. Hare GM, Tsui AK, Ozawa S, Shander A: Anaemia: Can we define haemoglobin thresholds for impaired oxygen homeostasis and suggest new strategies for treatment? Best Pract Res Clin Anaesthesiol 2013; 27:85–98
25. McLaren AT, Marsden PA, Mazer CD, Baker AJ, Stewart DJ, Tsui AK, Li X, Yucel Y, Robb M, Boyd SR, Liu E, Yu J, Hare GM: Increased expression of HIF-1alpha, nNOS, and VEGF in the cerebral cortex of anemic rats. Am J Physiol Regul Integr Comp Physiol 2007; 292:R403–14
26. Tsui AK, Marsden PA, Mazer CD, Adamson SL, Henkelman RM, Ho JJ, Wilson DF, Heximer SP, Connelly KA, Bolz SS, Lidington D, El-Beheiry MH, Dattani ND, Chen KM, Hare GM: Priming of hypoxia-inducible factor by neuronal nitric oxide synthase is essential for adaptive responses to severe anemia. Proc Natl Acad Sci U S A 2011; 108:17544–9
27. Mistry N, Mazer CD, Sled JG, Lazarus AH, Cahill LS, Solish M, Zhou YQ, Romanova N, Hare AGM, Doctor A, Fisher JA, Brunt KR, Simpson JA, Hare GMT: Red blood cell antibody-induced anemia causes differential degrees of tissue hypoxia in kidney and brain. Am J Physiol Regul Integr Comp Physiol 2018; 314:R611–22
28. Hare GMT, Han K, Leshchyshyn Y, Mistry N, Kei T, Dai SY, Tsui AKY, Pirani RA, Honavar J, Patel RP, Yagnik S, Welker SL, Tam T, Romaschin A, Connelly PW, Beattie WS, Mazer CD: Potential biomarkers of tissue hypoxia during acute hemodilutional anemia in cardiac surgery: A prospective study to assess tissue hypoxia as a mechanism of organ injury. Can J Anaesth 2018; 65:901–13
29. Klein AA, Collier TJ, Brar MS, Evans C, Hallward G, Fletcher SN, Richards T; Association of Cardiothoracic Anaesthetists (ACTA): The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK - The first Association of Cardiothoracic Anaesthetists national audit. Anaesthesia 2016; 71:627–35
30. Shander A, Javidroozi M, Naqvi S, Aregbeyen O, Caylan M, Demir S, Juhl A: An update on mortality and morbidity in patients with very low postoperative hemoglobin levels who decline blood transfusion (CME). Transfusion 2014; 54(10 pt 2):2688–95; quiz 2687
31. Weiskopf RB, Beliaev AM, Shander A, Guinn NR, Cap AP, Ness PM, Silverman TA: Addressing the unmet need of life-threatening anemia with hemoglobin-based oxygen carriers. Transfusion 2017; 57:207–14
32. Natanson C, Kern SJ, Lurie P, Banks SM, Wolfe SM: Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: A meta-analysis. JAMA 2008; 299:2304–12
33. LaPar DJ, Hawkins RB, McMurry TL, Isbell JM, Rich JB, Speir AM, Quader MA, Kron IL, Kern JA, Ailawadi G; Investigators for the Virginia Cardiac Services Quality Initiative: Preoperative anemia *versus* blood transfusion: Which is the culprit for worse outcomes in cardiac surgery? J Thorac Cardiovasc Surg 2018; 156:66–74.e2
34. Loor G, Rajeswaran J, Li L, Sabik JF III, Blackstone EH, McCrae KR, Koch CG: The least of 3 evils: Exposure to red blood cell transfusion, anemia, or both? J Thorac Cardiovasc Surg 2013; 146:1480–1487.e6
35. Roman MA, Abbasciano RG, Pathak S, Oo S, Yusoff S, Wozniak M, Qureshi S, Lai FY, Kumar T, Richards T, Yao G, Estcourt L, Murphy GJ: Patient blood management interventions do not lead to important clinical benefits or cost-effectiveness for major surgery: A network meta-analysis. Br J Anaesth 2021; 126:149–56
36. Wilson DF, Matschinsky FM: Metabolic homeostasis: Oxidative phosphorylation and the metabolic requirements of higher plants and animals. J Appl Physiol 2018; 125:1183–92
37. Prabhakar NR, Semenza GL: Oxygen sensing and homeostasis. Physiology (Bethesda) 2015; 30:340–8
38. Ragoonanan TE, Beattie WS, Mazer CD, Tsui AK, Leong-Poi H, Wilson DF, Tait G, Yu J, Liu E, Noronha M, Dattani ND, Mitsakakis N, Hare GM: Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. Anesthesiology 2009; 111:988–1000
39. Tsui AK, Marsden PA, Mazer CD, Sled JG, Lee KM, Henkelman RM, Cahill LS, Zhou YQ, Chan N, Liu E, Hare GM: Differential HIF and NOS responses to acute anemia: defining organ-specific hemoglobin thresholds for tissue hypoxia. Am J Physiol Regul Integr Comp Physiol 2014; 307:R13–25
40. Goodnough LT, Shander A: Patient blood management. Anesthesiology 2012; 116:1367–76
41. Dardashti A, Ederoth P, Algotsson L, Bronden B, Grins E, Larsson M, Nozohoor S, Zinko G, Bjurstein H: Erythropoietin and protection of renal function in cardiac surgery (the EPRICS Trial). Anesthesiology 2014; 121:582–90
42. Foroughi M, Mohammadi Z, Majidi Tehrani M, Bakhtiari M, Dabbagh A, Haji Molahoseini M: The effect of erythropoietin administration on the serum level of YKL-40, pro-BNP and IL-6 in coronary surgery patients. Iran J Pharm Res 2020; 19:430–9

43. Kim JH, Shim JK, Song JW, Song Y, Kim HB, Kwak YL: Effect of erythropoietin on the incidence of acute kidney injury following complex valvular heart surgery: A double blind, randomized clinical trial of efficacy and safety. Crit Care 2013; 17:R254
44. Weltert L, Rondinelli B, Bello R, Falco M, Bellisario A, Maselli D, Turani F, De Paulis R, Pierelli L: A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: Results of a prospective single-blind randomized controlled trial. Transfusion 2015; 55:1644–54
45. Yoo YC, Shim JK, Kim JC, Jo YY, Lee JH, Kwak YL: Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. Anesthesiology 2011; 115:929–37
46. Song YR, Lee T, You SJ, Chin HJ, Chae D-W, Lim C, Park K-H, Han S, Kim J-H, Na Y: Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: A pilot study. Am J Nephrol 2009; 30:253–60
47. Drexler C, Macher S, Lindenau I, Holter M, Moritz M, Stojakovic T, Pieber TR, Schlenke P, Amrein K: High-dose intravenous *versus* oral iron in blood donors with iron deficiency: The IronWoMan randomized, controlled clinical trial. Clin Nutr 2020; 39:737–45
48. Lin DM, Lin ES, Tran MH: Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: A systematic review. Transfus Med Rev 2013; 27:221–34
49. Richards T, Baikady RR, Clevenger B, Butcher A, Abeysiri S, Chau M, Macdougall IC, Murphy G, Swinson R, Collier T, Van Dyck L, Browne J, Bradbury A, Dodd M, Evans R, Brealey D, Anker SD, Klein A: Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): A randomised, double-blind, controlled trial. Lancet 2020; 396:1353–61
50. Hardy JF, Farmer SL, Auerbach M, Frank SM, Javidroozi M, Leahy MF, Meier J, Ozawa S, Shander A: Preoperative intravenous iron in anemic patients undergoing major abdominal surgery may not PREVENTT blood transfusions but still contribute to the objectives of patient blood management. Anesth Analg 2021; 132:1174–7
51. Cho BC, Serini J, Zorrilla-Vaca A, Scott MJ, Gehrie EA, Frank SM, Grant MC: Impact of preoperative erythropoietin on allogeneic blood transfusions in surgical patients: Results from a systematic review and meta-analysis. Anesth Analg 2019; 128:981–92
52. Kei T, Mistry N, Curley G, Pavenski K, Shehata N, Tanzini RM, Gauthier MF, Thorpe K, Schweizer TA, Ward S, Mazer CD, Hare GMT: Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: a systematic review and meta-analysis. Can J Anaesth 2019; 66:716–31
53. U.S. Food and Drug Administration: Information on erythropoiesis-stimulating agents (ESA) epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp). Available at: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-erythropoiesis-stimulating-agents-esa-epoetin-alfa-marketed-procrit-epogen-darbepoetin. Accessed May 29, 2021.
54. Spahn DR, Schoenrath F, Spahn GH, Seifert B, Stein P, Theusinger OM, Kaserer A, Hegemann I, Hofmann A, Maisano F, Falk V: Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: A prospective randomised trial. Lancet 2019; 393:2201–12
55. Hare GMT, Cazorla-Bak MP, Ku SFM, Chin K, Mistry N, Sklar MC, Pavenski K, Alli A, Van Rensburg A, Friedrich JO, Baker AJ, Mazer CD: 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. Can J Anaesth 2020; 67:1576–94
56. Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, Scott DA, Hare GMT, Jüni P, Mazer CD: Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: A meta-analysis. Eur Heart J 2019; 40:1081–8
57. Hovaguimian F, Myles PS: Restrictive *versus* liberal transfusion strategy in the perioperative and acute care settings: A context-specific systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2016; 125:46–61
58. Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, Carson JL, Cichutek K, De Buck E, Devine D, Fergusson D, Folléa G, French C, Frey KP, Gammon R, Levy JH, Murphy MF, Ozier Y, Pavenski K, So-Osman C, Tiberghien P, Volmink J, Waters JH, Wood EM, Seifried E; ICC PBM Frankfurt 2018 Group: Patient blood management: Recommendations from the 2018 Frankfurt Consensus Conference. JAMA 2019; 321:983–97
59. Mazer CD, Whitlock RP, Fergusson DA, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, Carrier FM, McGuinness S, Young PJ, Byrne K, Villar JC, Royse A, Grocott HP, Seeberger MD, Mehta C, Lellouche F, Hare GMT, Painter TW, Fremes S, Syed S, Bagshaw SM, Hwang NC, Royse C, Hall J, Dai D, Mistry N, Thorpe K, Verma S, Jüni P, Shehata N; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group: Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. N Engl J Med 2018; 379:1224–33
60. Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, Liang X, Jiang G, Liu Z, Li X, Zuo L, Luo L, Wang J, Zhao MH, Liu Z, Cai GY, Hao L, Leong R, Wang C, Liu C, Neff T, Szczech L, Yu KP: Roxadustat treatment for anemia in patients undergoing long-term dialysis. N Engl J Med 2019; 381:1011–22

61. Chen N, Hao C, Peng X, Lin H, Yin A, Hao L, Tao Y, Liang X, Liu Z, Xing C, Chen J, Luo L, Zuo L, Liao Y, Liu BC, Leong R, Wang C, Liu C, Neff T, Szczech L, Yu KP: Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med 2019; 381:1001–10

62. Zheng Q, Yang H, Sun L, Wei R, Fu X, Wang Y, Huang Y, Liu YN, Liu WJ: Efficacy and safety of HIF prolyl-hydroxylase inhibitor vs epoetin and darbepoetin for anemia in chronic kidney disease patients not undergoing dialysis: A network meta-analysis. Pharmacol Res 2020; 159:105020

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

The Circle of Life: Christopher Wren and the First Intravenous Anesthetic

When royal physician William Harvey published his magnum opus, *De Motu Cordis* (1628), he dismantled 15 centuries of European allegiance to Galen's belief that blood originated in the liver, trickled out through veins, and was consumed by the tissues. According to Harvey, the heart pumped blood that was conserved as it circulated through the body. Almost 30 years later, Christopher Wren (1632 to 1723), astronomer and future architect of today's St. Paul's Cathedral (*upper right*), sought to prove Harvey's controversial theory by showing that drugs entering the bloodstream would quickly reach the heart and brain. In 1656, Wren convened with two friends from his Oxford circle—the great chemist Robert Boyle and physician Thomas Willis—at Boyle's High Street Home. In their best-known experiment, Wren fastened the legs of Boyle's dog to the corners of a table (*left*), cut into its limb to isolate a vein, and infused opium (*lower right*) and wine through a goose quill connected to a pig bladder that contained the elixir. As soon as the dog was freed, he "appear'd…stupifi'd" and crumpled to the floor, having become the recipient of the world's first intravenous anesthetic. Wren and Willis would later use intravascular injections to delineate yet another famed anatomic circuit—the brain's arterial "Circle of Willis." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

Jane S. Moon, M.D., University of California, Los Angeles, California, and Melissa L. Coleman, M.D., Penn State College of Medicine, Hershey, Pennsylvania.