NARRATIVE REVIEW ARTICLE

Perioperative Quality Initiative and Enhanced Recovery After Surgery-Cardiac Society Consensus Statement on the Management of Preoperative Anemia and Iron Deficiency in Adult Cardiac Surgery Patients

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Preoperative anemia is common in patients presenting for cardiac surgery, with a prevalence of approximately 1 in 4, and has been associated with worse outcomes including increased risk of blood transfusion, kidney injury, stroke, infection, and death. Iron deficiency, a major cause of anemia, has also been shown to have an association with worse outcomes in patients undergoing cardiac surgery, even in the absence of anemia. Although recent guidelines have supported diagnosing and treating anemia and iron deficiency before elective surgery, details on when and how to screen and treat remain unclear. The Eighth Perioperative Quality Initiative (POQI 8) consensus conference, in conjunction with the Enhanced Recovery after Surgery-Cardiac Surgery Society, brought together an international, multidisciplinary team of experts to review and evaluate the literature on screening, diagnosing, and managing preoperative anemia and iron deficiency in patients undergoing cardiac surgery, and to provide evidence-based recommendations in accordance with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria for evaluating biomedical literature. (Anesth Analg 2022;135:532–44)

GLOSSARY

AWP = average wholesale price in US dollars; **EMR** = electronic medical record; **CBC** = complete blood count; **CI** = confidence interval; **CKD** = chronic kidney disease; **ERAS-CS** = Enhancing Recovery After Surgery-Cardiac Society; **ESA** = erythropoietin stimulating agents; **GRADE** = Grading of Recommendations, Assessment, Development and Evaluation; **H&P** = History & Physical; **Hb** = hemoglobin; **ICU** = intensive care unit; **IDA** = iron-deficiency anemia; **IV** = intravenous; **LMW** = low molecular weight; **LOE** = level of evidence; **LOS** = length of stay; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **PBM** = patient blood management; **PO** = per os; **POC** = point of care; **POQI** = Perioperative Quality Initiative; **RBC** = red blood cells; **STS/SCA/AmSECT/SABM** = Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of ExtraCorporeal Technology/Society for the Advancement of Blood Management; **TDI** = total dose infusion; **WHO** = World Health Organization

Effective patient blood management (PBM) remains an integral component of the optimal care of cardiac surgical patients. The recent Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of ExtraCorporeal Technology/Society for the Advancement of Blood Management (STS/SCA/AmSECT/SABM) Update to the Clinical Practice Guidelines on Patient Blood Management[1] provides guidance on several key areas including optimizing coagulation and interdisciplinary blood conservation modalities. Another key element of PBM is the management of preoperative anemia, which is present in approximately 1 in 4 patients undergoing nonemergent cardiac surgery.[2–4] Preoperative anemia is independently associated with worse outcomes, including mortality, and associated with blood product transfusion, with its associated risks.[5,6] This is of particular

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importance to the aging cardiac surgery patient population, who have high rates of anemia and thus red blood cell (RBC) transfusion risk.[7]

Anemia optimization and transfusion avoidance is observed in patients who decline blood products for personal or religious reasons. Many have argued that the techniques used to manage these patients should be more broadly applied.[8] While both the recent aforementioned update[1] and Enhanced Recovery After Surgery-Cardiac Society (ERAS-CS) guidelines[9] have provided the recommendations that preoperative identification of anemia and its antecedent causes should be investigated, key considerations such as timing, dosing and agent(s) to be used remain unclear. In the recent ERAS-CS guidelines, it was recognized that preoperative anemia is common and associated with poor outcomes in patients undergoing noncardiac surgery, yet "…the data supporting improved outcomes in the literature on [cardiac surgery was] weak."[9] Tibi et al[1] have recommended the use of erythropoietin stimulating agents (ESA) and iron supplementation in the preoperative phase, but did not provide details on the effective implementation of this approach. Furthermore, the identification of potential barriers to the use of these agents and cost-effectiveness requires additional consideration. Therefore, the objective of this initiative was to provide clinicians and investigators practical guidance in keys areas related to the management of anemia in the preoperative cardiac surgery patient, using a modified Delphi process and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.[10,11]

METHODOLOGY

The Perioperative Quality Initiative (POQI) is a nonprofit organization that assembles international, multidisciplinary teams to develop consensus-based recommendations on perioperative medicine.[12] The POQI methodology combines elements of both evidence appraisal and expert opinion, while acknowledging the limitations of available literature to provide practical recommendations. The eighth POQI meeting convened with the Cardiac ERAS Society between October 20 and 22, 2021, in Sacramento, CA, to address perioperative issues with cardiac surgery. Three separate working groups with expertise in blood management, acute kidney injury, and opioid use were created. Before the meeting, group members were assembled to include multidisciplinary representation from surgery, anesthesiology, nursing, and critical care, with experts from the United States, Canada, and the United Kingdom. Led by 2 co-chairs, group members performed individual electronic literature searches to generate bibliographies of relevant articles before the meeting. Questions regarding controversies in the field or where there was a lack of consensus were identified by all group members and compiled and finalized by the group chairs (N.R.G. and E.B.-G. for blood management group). Four predetermined questions were addressed by the blood management working group: (1) How should patients undergoing nonemergent cardiac surgery be evaluated for preoperative anemia in terms of timing and necessary laboratory studies? (2) For anemic patients identified before nonemergent cardiac surgery, how should anemia be treated? (3) What are the barriers to identifying and treating anemia in cardiac surgery patients and how can they be mitigated? (4) What is the financial impact of preoperative anemia management for cardiac surgery patients (does the cost of care result in cost savings in terms of transfusion avoidance or other improved outcomes)? Literature pertaining to the above questions was assembled before the meeting and reviewed across the working group. Sampling and selection of the literature was performed through a PubMed search using the terms including "preoperative anemia," "iron deficiency," "patient blood management," and "cardiac surgery" and excluding case reports, editorials, and commentaries, or articles not published in the English language.

A Modified Delphi process was utilized in the construction of the recommendations as described in prior POQI consensus statements.[11,12] Over the 3 days of the meeting, questions were refined and recommendations developed via 4 plenary sessions and 3 small group sessions. Voting was conducted openly during conference plenary sessions, which included the entirety of conference members reviewing each working group's statements. While partiality, influence, and bias cannot be excluded completely during the voting, the plenary session moderators actively encouraged dissenting opinions to be presented. Dissenting opinions were recognized and accounted for, and any debates over disagreeing opinions helped expand group knowledge and awareness on issues associated with a drafted consensus statement. These iterative sessions served to solidify the consensus statements. The strength of evidence and recommendations were established using the GRADE methodology.[10,13,14] During the final POQI conference session, all members from all 3 working groups voted to agree or disagree with the statements and recommendations (Table 1). Voting was recorded for transparency (Supplemental Digital Content 1, Supplement 1, http://links.lww.com/AA/E8), and if there were any dissenting votes, an accompanying dissenting opinion was included in the manuscript, although the goal was to achieve unanimous consensus. Difference of opinion as to the strength of the evidence was also voted on and

Table 1. POQI 8 Consensus Statements and Recommendations

		Strength[a]	LOE[b]
Statement 1.1	We recommend screening all patients for anemia and iron deficiency as soon as surgery is contemplated.	Strong	B
Statement 1.2	We recommend measurement of hemoglobin concentration as a screening tool for anemia.	Strong	A
Statement 1.3	We recommend measurement of ferritin and transferrin saturation as a screening tool for iron deficiency.	Strong	B
Statement 1.4	We recommend further work-up for patients identified as being anemic to determine etiology and appropriate treatment (laboratory work-up including CBC, if anemia identified by POC testing, creatinine, vitamin B12, folate, reticulocyte count, H&P).	Strong	B
Statement 2.1	We recommend preoperative treatment for anemia.	Strong	B
Statement 2.2	We recommend preoperative treatment of iron deficiency with or without anemia.	Strong	C
Statement 2.3	We recommend treatment of iron-deficiency anemia with intravenous iron preferred over oral iron when there is limited time before surgery.	Strong	B
Statement 2.4	We recommend referral for consideration of erythropoietin stimulating agents treatment for the following patient populations: patients who decline red cell transfusion, have moderate to severe anemia, or have anemia secondary to chronic kidney disease and/or anemia of chronic inflammation.	Strong	B
Statement 3.1	We recommend the use of a structured clinical pathway to evaluate and treat preoperative anemia in cardiac surgery.	Strong	B
Statement 3.2	We recommend leveraging the EMR to provide alerts to clinicians to identify patients who are anemic before surgery and prompt further evaluation.	Weak	C
Statement 4.1	We recommend the use of a preoperative anemia care coordination program as a cost-effective method to improve outcomes.	Weak	C

Abbreviations: CBC, complete blood count; EMR, electronic medical record; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; H&P, History & Physical; LOE, level of evidence; POC, point of care; POQI, Perioperative Quality Initiative.

[a]Strength of recommendation per GRADE process.

[b]LOE per GRADE process.

recorded during the voting period (Supplemental Digital Content 1, Supplement 1, http://links.lww.com/AA/E8). Of note, no dissenting opinions were encountered with voting sessions on the following recommendations.

SUMMARY OF RECOMMENDATIONS AND SUPPORTING EVIDENCE

Question 1: How Should Patients Undergoing Nonemergent Cardiac Surgery Be Evaluated for Preoperative Anemia in Terms of Timing and Necessary Laboratory Studies?

Anemia and iron deficiency represent 2 distinct, but often concurrent, clinical diseases that warrant attention in the patient awaiting cardiac surgery. The prevalence of anemia in patients undergoing cardiac surgery has been estimated to range from 20% to 30%, and roughly 30% to 80% of these anemic patients suffer from an iron-deficiency anemia (IDA).[2,15,16] Anemia before cardiac surgery has been associated with an increase in transfusion risk, postoperative morbidity, and mortality.[2–4]

Iron deficiency may also present as an isolated disease without anemia during laboratory screening before cardiac surgery. Nonanemic iron deficiency has been estimated to occur in around 20% of patients scheduled for cardiac surgery (Figure 1).[17–19] Nonanemic iron deficiency has emerged as a risk factor for outcomes following cardiac surgery. Patients with nonanemic iron deficiency undergoing cardiac surgery may have lower postoperative hemoglobin (Hb) levels, and be more likely to receive allogeneic transfusions and experience complications and prolonged hospital stay.[17,19]

Management of anemia and iron deficiency should follow the model of perioperative medicine, where integrated medical care begins from the moment that surgery is contemplated.[20] The time between contemplation of surgery to the identification of anemia, which may differ globally across health systems, should be minimized. Prompt screening and evaluation of anemia before cardiac surgery permits timely administration of therapies to treat underlying disease states and prevent postoperative complications. In some cases, additional time for referral to specialists like hematologists is necessary to elucidate less common disease states amenable to preoperative therapy. Therapeutic efficacy with iron replacement is time-dependent and varies with the severity of deficiency and pharmacologic preparations used. For example, intravenous (IV) iron replacement can raise Hb in IDA by 1 to 2 g/dL over 2 to 4 weeks, depending on the specific preparation.[21,22] Therefore, with relation to timing, we recommend screening all patients for anemia and iron deficiency as soon as surgery is contemplated, preferably 4 or more weeks before surgery.

Anemia has been described as a clinical syndrome of "blood failure" associated with decreased RBC mass and oxygen delivery to tissues. Laboratory measurement of Hb concentration continues to serve as the surrogate for RBC mass in the diagnosis of anemia, given the ease of measuring the former over the latter.[23] The World Health Organization (WHO) defined anemia in 1968 as Hb concentrations below 13 g/dL in men and concentrations below 12 g/dL in women.[24] These values were derived from small studies in primarily northern European individuals, with minimal documentation on the sampling

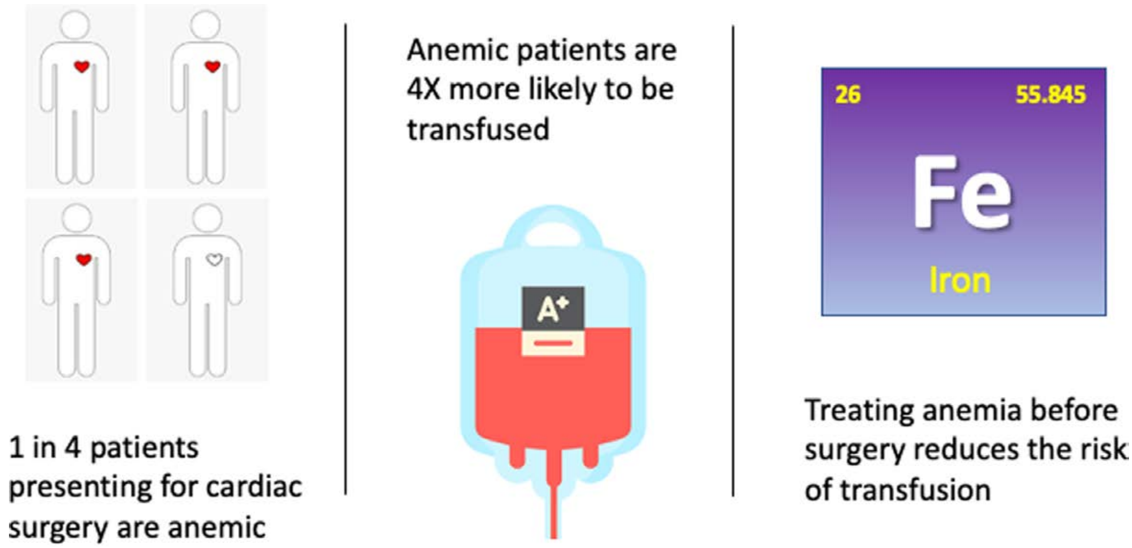

Figure 1. Summary of anemia prevalence and association with transfusion in cardiac surgery patients. Figure reused with permission from the Perioperative Quality Initiative.

methodology for the Hb concentration distribution.[25] Though the WHO definition for anemia has served as the foundation for numerous studies on PBM, alternative thresholds have been proposed. For example, 1 study in patients undergoing orthopedic surgery revealed female patients receive nearly twice as many transfusions as males using the WHO anemia thresholds.[26] Utilizing a single preoperative anemia threshold defined by a Hb concentration below 13 g/dL may be more appropriate than WHO criteria, and would result in more female patients being diagnosed with anemia preoperatively that should be treated to reduce perioperative transfusions.[23,26] Although normal Hb distributions may vary with factors such as age, ethnicity, and physiologic factors, for example, dwelling at high altitudes or pregnancy,[25,27] the benefit of tailoring anemia cutoffs to specific cardiac surgery subpopulations remains uncertain. Nonetheless, we recommend measurement of Hb concentration as a screening tool for anemia.

Iron deficiency is a prevalent condition across both anemic and nonanemic patients undergoing cardiac surgery. About 30% to 80% of cardiac surgery patients with preoperative anemia have IDA, and an additional 20% to 50% of nonanemic cardiac surgery patients possess an iron deficiency.[15,16,21] The presence of iron deficiency with or without anemia has been associated with lower postoperative Hb levels, increased transfusion requirements, and mortality.[17,19] The results of a prospective observational study analyzing 730 patients undergoing elective cardiac surgery found patients with preoperative iron deficiency had a 3-fold risk in 90-day mortality.[19]

Laboratory demonstration of IDA classically rests on detection of low circulating iron levels, transferrin saturation, and ferritin levels. Indeed, low serum ferritin levels are characteristic for an absolute iron deficiency.[28] Patients undergoing cardiac surgery may present with nonanemic iron deficiency in the setting of a negative iron balance. Over time, the negative iron balance can evolve into an absolute deficiency with resultant iron-restricted erythropoiesis.[29] Low ferritin levels correlate strongly with reduced stainable iron from bone marrow in patients without inflammation. When inflammation and comorbidities are present, serum ferritin levels may fail to drop below the typically used 30 µg/L cutoff owing to ferritin's role as an acute phase reactant. Consequently, a ferritin level below 100 µg/L combined with a reduced transferrin saturation below 20% has been recommended to diagnose iron deficiency.[28,30]

Several studies investigating the impact of iron deficiency with or without anemia have used a serum ferritin cutoff of 100 µg/L.[17,19,21,31] One study found that a ferritin level below 100 µg/L identified low iron stores with a sensitivity (64.9%) and specificity (96.1%) against the gold standard bone marrow hemosiderin staining.[32] However, when tested against the gold standard of a functional response to IV iron, both the sensitivity and specificity dropped by roughly 20% using the same ferritin threshold. Transferrin saturation demonstrated a better sensitivity (59%–81%) and specificity (63%–78%) for detecting a functional response to iron therapy as compared with ferritin alone.[30] The combined measurement of ferritin and transferrin saturation as part of routine iron deficiency screening may therefore offer a superior strategy over ferritin or transferrin alone. Additional measurements, like mean corpuscular volume, reticulocyte Hb content, hepcidin, percent hypochromic

RBCs, soluble transferrin receptor, ferritin index, and C-reactive protein may all serve to provide a comprehensive assessment for iron-restricted erythropoiesis.[23,29] Therefore, in light of the above, we recommend measurement of ferritin and transferrin saturation as an initial screening tool for iron deficiency.

Anemia identified preoperatively warrants evaluation for underlying conditions amenable to treatment. In the cases where IDA has been identified, timely evaluation for the cause should occur. Gastrointestinal blood loss, potentially from a serious underlying pathology, remains a common cause for iron deficiency in men and postmenopausal women.[33,34] Multifactorial anemias, however, are likely in the elderly, malnourished, and in patients suffering chronic inflammatory states. In such individuals, other underlying conditions beyond iron deficiency should be treated to ensure that the anemia resolves while iron levels are restored.[35] When anemia presents along with thrombocytopenia or leukopenia, further investigation for a blood dyscrasia should occur ideally in consultation with a hematologist. If newly diagnosed renal disease accompanies an anemia, then referral to a nephrologist should occur.[23] Therefore, we recommend further work-up for all patients identified as being anemic to determine the etiology and appropriate treatment.

Question 2: For Anemic Patients Identified Before Nonemergent Cardiac Surgery, How Should Anemia Be Treated?

Once anemia has been identified, the question remains if and how to treat it before nonemergent cardiac surgery. Preoperative anemia is associated with worse perioperative outcomes, including increased risk of infection, stroke, acute kidney injury, and mortality,[2–4] as well as being a strong predictor of perioperative transfusion.[26,36] Although there is limited evidence demonstrating that treating anemia preoperatively reduces complications other than transfusion, there is significant reduction in transfusion if anemia is effectively treated before surgery.[31,37,38] Due to the costs and potential risks associated with transfusion, transfusion reduction alone may be sufficient reason to treat anemia before elective surgery. As more recent studies suggest, additional benefits to treating anemia, for example, reduced length of stay (LOS)[39] and risk of readmission,[40] the rationale to treat anemia preoperatively increases. We recommend that anemia should be treated before elective surgery to decrease perioperative transfusion and mitigate additional associated risks (Figure 2).

Additionally, to optimize RBC mass throughout the perioperative period, we recommend treatment of iron deficiency, with and without anemia, before surgery. Iron deficiency is common in patients presenting for elective cardiac surgery and has been associated with worse perioperative outcomes.[19,39] Adequate iron stores are needed to recover from postoperative blood loss and allow for regeneration of RBCs. Cardiac surgery is associated with a significant loss of RBC mass, and without adequate iron stores, patients will be unable to mount a hemopoietic response postoperatively. Additionally, the postsurgical inflammatory state may further inhibit RBC production,[33] rendering postoperative treatment less effective.

Options for Treatment: Oral and IV Iron. If time allows (eg, at least 6 weeks), oral iron is the preferred treatment for preoperative anemia/iron deficiency as it is inexpensive and readily available. Oral iron formulations include ferrous salts, such as ferrous sulfate and ferrous gluconate, and other formulations such as ferric citrate and polysaccharide iron complexes.[41] Dosing is usually based on the amount of elemental iron, with doses ranging from 60 to 200 mg. For example, oral ferrous sulfate has 65 mg of elemental iron per 325 mg tablet. Oral iron formulations are typically dosed every other day, as this has been shown to be as effective as daily dosing with fewer side effects, since daily dosing leads to decreased absorption due to elevated levels of hepcidin.[42] However, even with consecutive day dosing, bioavailability remains poor, with less than a quarter of the iron absorbed.[42] Additionally, absorption of oral iron is inhibited by inflammatory states, concomitant use of proton-pump inhibitors, and ingestion of tannins (such as in tea) and calcium.[43] Due to the numerous gastrointestinal side effects with oral iron, patient compliance is low,[44] and even if it is tolerated, it can take months of supplementation to fully replete iron stores, a time period that many patients needing cardiac surgery cannot wait.

Multiple studies have demonstrated the superiority of IV iron over oral iron to rapidly replete iron stores and increase Hb.[45–47] There are numerous formulations of IV iron available, some of which can replete iron stores in a single dose (total dose infusion [TDI]), and all of which have similar safety and efficacy.[43] There are considerable differences in the cost of the various formulations (Table 2), with the newer formulations offering TDI that can be given quickly, but at a higher price. The choice between formulations is made primarily by availability, patient insurance, and patient preference regarding number of required infusions and calculated iron deficit. The appropriate dose can be calculated using the Ganzoni formula,[50] however, it is common to simply administer 1 g of IV iron to replete stores, then reassess for additional dosing if needed.

IV iron can be given in the outpatient setting, although it requires an IV catheter and appropriate monitoring. With high molecular weight iron dextran

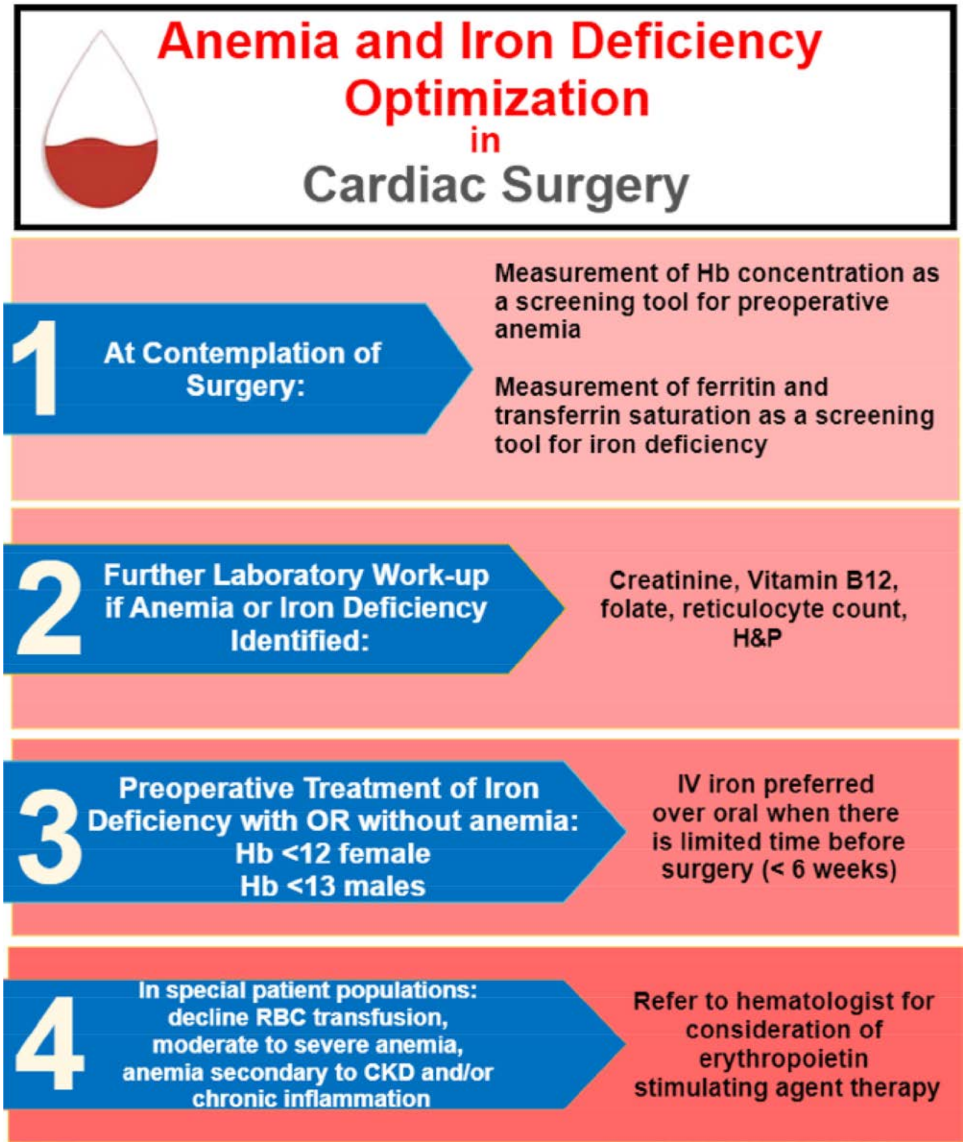

Figure 2. Anemia treatment algorithm. Figure reused with permission from the Perioperative Quality Initiative. CKD indicates chronic kidney disease; H&P, History & Physical; Hb, hemoglobin; IV, intravenous; RBC, red blood cells.

Table 2. Iron formulations summary[43,48]

Formulation	Route	Dosing	Number of infusions[a]	AWP	Estimated cost/1000 mg	Additional considerations
Ferrous sulfate	PO	325 mg	N/A	$0.78/tablet	N/A	Limited absorption, significant gastrointestinal side effects
Iron sucrose	IV	200 mg	5	$16.90 (2.5 mL vial)	$338	Requires multiple doses
LMW Iron Dextran	IV	1000 mg	1	$28.79 (2 mL vial)	$288	Requires test dose, longer infusion time
Ferric gluconate	IV	125 mg	8	$7.27 (5 mL vial)	$582	May be given as IV push, requires multiple doses
Ferumoxytol	IV	510 mg	2	$327.75 (17 mL vial)	$655	May affect MRI
Ferric derisomaltose	IV	1000 mg	1	$2464.27 (10 mL vial)	$2464	Short infusion time
Ferric carboxymaltose	IV	750 mg	1.3	$885.84 (15 mL vial)	$1329	Risk of hypophosphatemia

Abbreviations: AWP, average wholesale price in US dollars[49]; IV, intravenous; LMW, low molecular weight; MRI, magnetic resonance imaging; PO, per os.
[a]To replete with a total of 1000 mg iron, which is a routine dose for all the formulations.

no longer in use, allergic reactions from the available formulations are rare, although sensitivity reactions related to the labile free iron may occur and include symptoms such as flushing, chest tightness, and myalgias, without accompanying shortness of breath or edema, and which are usually self-limited and do not require treatment.[43] Treatment with IV iron can typically improve Hb within 2 to 4 weeks, after which Hb and ferritin can be rechecked to assess response and need for additional therapy.[51]

For patients with <6 weeks before surgery, or for patients unable to tolerate oral iron, we recommend treating IDA with IV iron due to the more rapid restoration of iron stores with IV iron.

Options for Treatment: ESAs. Hesitation toward the use of ESAs in cardiac surgery patients stems primarily from the United States Food and Drug Administration's Black Box Warning, which warns of increased risk of thrombosis and mortality. These risks are likely mitigated when ESAs are limited to a short perioperative course, and recent data suggest that treatment of preoperative anemia with a brief course of ESAs reduces transfusion without increased risk of thrombosis in cardiac surgical patients.[31,38] Nonetheless, routine use remains controversial, with some clinical practice guidelines supporting their use in cardiac surgery[1] while others do not.[52] There are certain patients more likely to benefit from use of ESAs to correct anemia, for whom treatment should be considered, and we recommend referral for consideration of ESA treatment for select patient populations. Patients who decline RBC transfusion are at increased risk of organ ischemia and mortality with severe anemia,[53] and therefore may warrant treatment to higher Hb levels before major surgery.[8] Additionally, patients with anemia secondary to chronic kidney disease or anemia of inflammation, and underlying bone marrow suppression, may benefit from treatment.[23] Finally, patients with moderate to severe anemia should be referred to a specialist for anemia management and consideration of ESAs, as they may be at higher risk for transfusion, and the benefits of treating these patients may outweigh the potential risks.[33]

Question 3: What Are the Barriers to Identifying and Treating Anemia in Cardiac Surgery Patients and How Can They Be Mitigated?

While we propose that it is worthwhile to identify and treat anemia before elective cardiac surgery, we acknowledge that there are potential barriers to implementation. Studies examining this have summarized the key barriers to be access to knowledge and information, patient needs and resources, knowledge and beliefs, available resources, and networks and communications.[54]

We have summarized the main barriers to diagnosis and treatment of anemia in cardiac surgery, listed chronologically, as follows (Figure 3):

1. Culture (acknowledging anemia as a modifiable risk factor)
2. Educational gaps (types of anemia and time required to diagnose and correct)
3. Inadequate measurement
4. Time to optimize
5. Availability of resources

The first barrier involves adapting the institutional culture to accept anemia as a modifiable risk factor that should be prioritized as an element of preoperative care in elective cardiac surgery. Numerous randomized controlled studies demonstrating similar outcomes in patients with restrictive versus liberal transfusion strategies may have led to a general acceptance of the overall safety of transfusion,[55–58] prompting physicians to simply treat anemia with transfusion. Although the risks associated with allogeneic blood may be mitigated with restrictive transfusion strategies and leukoreduction of blood products, they remain a limited resource with associated costs, which has been highlighted during the recent blood shortage. Cultivating recognition on the importance of a thorough preoperative anemia assessment and treatment course preoperatively as opposed to using transfusion as the first line of treatment is essential. Changing culture requires education on the risks of anemia, and the benefits of addressing it, for patients, physicians, and administrators.

A related barrier to implementation is the educational gap surrounding the types and treatment of anemia. Educational gaps related to anemia appear to be common,[59] and are related to logistics of anemia screening, types of anemia, management of anemia with oral iron versus IV iron supplementation, and use of ESAs. There are also gaps concerning postoperative anemia management. Addressing these gaps requires structured educational programs.

Another barrier relates to inadequate screening for anemia. Many patients do not have routine laboratory studies until a day or 2 before surgery, and even when a patient is identified as having anemia, further testing and diagnosis of cause are incomplete.[60] To avoid missing the opportunity to evaluate anemia once recognized, it is possible to draw all necessary laboratory studies at the time of initial anemia screening, and only run the additional tests if and when anemia is identified, through leveraging the electronic medical record (EMR).[61] The EMR can also be used to prompt for anemia evaluation as soon as surgery is scheduled, and in institutions that have it, we recommend leveraging the EMR to provide alerts to clinicians to identify patients who are anemic before surgery and prompt further evaluation.

Inadequate time for optimization preoperatively is a major barrier to treating anemia before cardiac surgery, and in some countries, for example, United States, is probably the most significant. In some settings, market and competitive pressures may play a role as there may be concern that allowing a longer preoperative duration may increase the likelihood

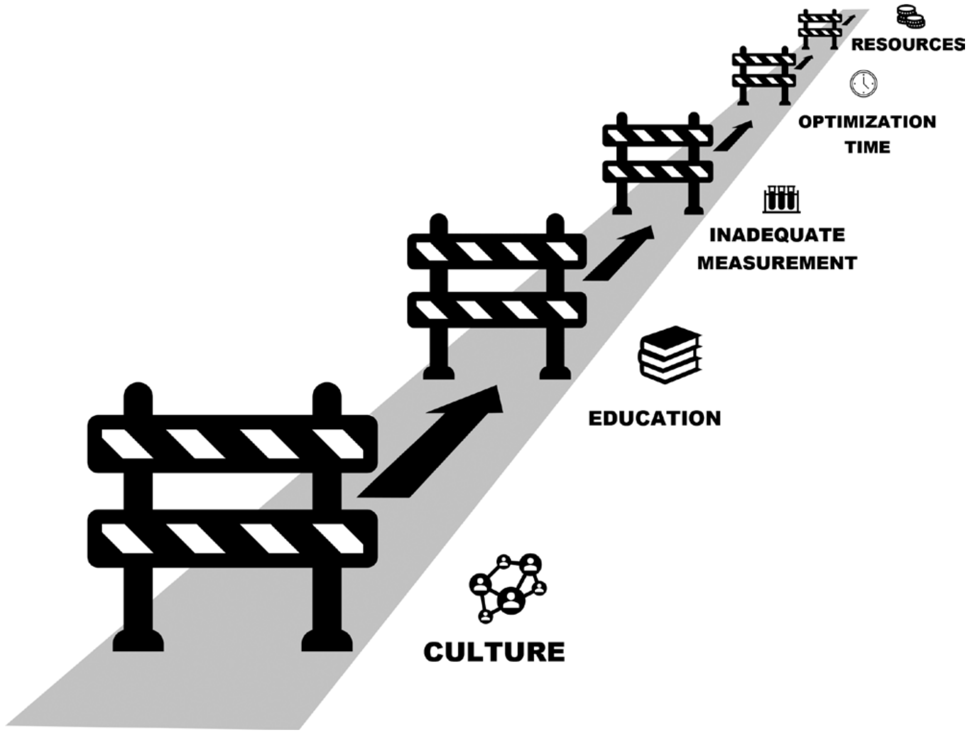

Figure 3. Barriers to addressing preoperative anemia. Figure reused with permission from the Perioperative Quality Initiative.

that the patient will cancel surgery or seek treatment with a competitor. Another reason a surgeon may want to do surgery as quickly as possible is concern that a delay may lead to worse outcome for the patient, for example, death or deterioration before surgery. Unfortunately, there are limited data regarding how delaying cardiac surgery affects outcomes. Indirect evidence comes from countries with centralized health systems, where waitlists for elective procedures are common.[62] One study comparing patients who had urgent cardiac surgery versus those who waited a mean time of 2.8 months for elective surgery showed no difference in in-hospital mortality or LOS among a retrospective cohort of 568 patients, despite other differences between the 2 groups. Another study of over 2000 patients found a 0.7% risk of death while waiting for cardiac surgery, but no increased risk of death associated with prolonged wait times.[63] Among patients with stenosis of the left main coronary artery awaiting cardiac surgery, the authors of one study of 561 patients concluded that there did not appear to be an association between wait times and morbidity or mortality.[64] Of note, a subset of these 561 patients, who waited out of the hospital for surgery, had a median wait time of 30 to 49 days.[64] Several studies have tried to determine risk factors for increased mortality with delaying surgery, to better identify which patients could wait without adverse consequences.[65] A retrospective study in Canada of over 12,000 patients showed that 0.8% of patients died while waiting for cardiac surgery, and risk factors for death while on the waitlist included age, aortic surgery, decreased ejection fraction, urgent surgery, prior myocardial infarction, hemodynamic instability during cardiac catheterization, hypertension, and dyslipidemia.[66] Being able to identify which patients are at risk of adverse outcomes associated with waiting may help determine the risks and benefits of proceeding directly to surgery versus undergoing preoperative optimization.

Despite studies showing decreased transfusion with treatment of anemia only days before surgery,[31,67] it usually takes weeks to months to see the full benefit of anemia treatment. Ideally, patients should be evaluated as early as possible to allow adequate time for diagnosis and treatment.[68] Capturing patients earlier, at the time surgery is contemplated, may allow for adequate time to address these needs. Use of a structured clinical pathway may increase the likelihood of success, as evidenced through the work involved setting up PBM pathways,[21] and we recommend the use of a structured clinical pathway to evaluate and treat preoperative anemia in cardiac surgery.

Finally, to leverage the EMR and create a structured clinical pathway/program, resources from the institution are required. Engaging with stakeholders to capture data and demonstrate the cost-effectiveness of these programs is necessary to secure resources and grow a successful program.[69]

Question 4: What Is the Financial Impact of Preoperative Anemia Management for Cardiac Surgery Patients (Does the Cost of Care Result in Cost Savings in Terms of Transfusion Avoidance or Other Improved Outcomes)?

Cost-effectiveness is primarily an indirect measurement, derived from measuring variables and metrics that drive total cost of care. These variables include transfusion rate and volume, hospital LOS, intensive care unit (ICU) LOS, ICU cost of care, discharge disposition and unplanned 30-day readmission. Additional costs include costs associated with management of transfusion and transfusion-related risks (eg, transmitted infections). Finally, it should be noted that there is value (cost avoidance) attributed to patient and/or surgeon satisfaction associated with transfusion avoidance that is often implied but rarely measured. The following discussion focuses on cost to the institution, however, it is recognized that costs incurred by both patients and insurers are also important.

Financial modeling to implement a preoperative anemia management program has been reported, highlighting key direct and variable costs for hospital implementation of an anemia management program, including staffing, equipment, laboratory assays, facilities, and medications.[70] In this model, implementation costs were minimized by utilizing preexisting clinical spaces within the hospital to avoid significant facility costs. An example estimate for hospital implementation costs, extracting direct and variable cost data from the previous model, is provided in Table 3. Exact costs, however, will likely vary by institution, location, and staffing requirements. Two different annual cardiothoracic surgery case volumes are provided to demonstrate impacts by variable costs associated with case volume. An IV iron therapy course was estimated to cost approximately $300 USD, though treatment courses could be as high as $2500 USD depending on the preparation (Table 2). The prevalence of iron deficiency warranting IV iron therapy was estimated to range from 20% to 64%.

Actual preoperative anemia management cost-effectiveness data are limited. Among the few data that exist, cost-effectiveness data reflect metrics that are typically extracted from hospital clinical costing systems, and capture net cost of care, direct variable cost of care, and/or total costs at the admission level and/or post discharge level (all adjusted or nonadjusted). Direct cost considers fixed costs for maintaining a care coordination program (ie, staffing) as well as therapeutic options (ie, IV iron formulation choice and use of ESAs), whereas variable costs include items such as diagnostic laboratories for the patient and the hospital. Cost-effectiveness or the return on investment considers direct and variable cost of care as well as direct contribution margin and cost avoidance for the total episodic cost of care. Data on cost-effectiveness are summarized below and demonstrate varying impact on transfusion and limited data on length of stay, readmission, and cost of care.

In 2008, the Western Australia Department of Health initiated a health-system–wide blood management program. In a retrospective study of 605,046 patients admitted to 4 adult tertiary-care hospitals between July 2008 and June 2014, comparison of final year with baseline, demonstrated units of RBCs, fresh frozen plasma, and platelets transfused per admission decreased 41% (P < .001).[71] The authors concluded that this decrease in product transfusion represented an estimated activity-based savings of between AU$80 to 100 million (US$78–97 million). The reduction in transfusion was also associated with risk-adjusted reductions in-hospital mortality (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.67–0.77; P < .001), length of stay (incidence rate ratio, 0.85; 95% CI, 0.84–0.87; P < .001), hospital acquired infections (OR, 0.79; 95% CI, 0.73–0.86; P < .001), and acute myocardial infarction-stroke (OR, 0.69; 95% CI, 0.58–0.82; P < .001). They concluded that implementation of a blood management program was associated with improved outcomes, reduced blood product utilization, and product-related cost savings. A major limitation of this analysis is that a historical control group (several years change in practice) was used, therefore, it is not known if the improvement in outcomes/cost savings was caused by the decrease in transfusion or to other factors which undoubtedly changed during this time.

More rigorous evidence, albeit in noncardiac surgical patients, comes from a 2020 randomized controlled trial that compared the use of 1000 mg IV ferric carboxymaltose with placebo 10 to 42 days before major open abdominal surgery in 388 patients (per-protocol analysis) with anemia (defined as Hb <13.0 mg/dL for men, and <12.0 mg/dL for women).[40] The authors reported no significant differences between groups for any end points and reported similar mean time from treatment to surgery in each group. The authors, however, reported that anemia was corrected in only 21% of patients who received IV iron, calling into question the efficacy of IV iron treatment, and they did not evaluate for etiology of anemia before treatment. These authors reported that readmission to the hospital following surgery was significantly lower in the first 8 weeks after surgery (13% vs 22%, rate ratio 0.54, 95% CI, 0.3–0.85) as well as at 6 months (26% vs 32%, rate ratio 0.64, 95% CI, 0.4–0.92) in the group who received IV iron.

In a retrospective analysis, it was reported that targeted preoperative anemia management with IV iron in elective colorectal surgery was associated with reductions in RBC transfusions and LOS.[72] In

Table 3. Financial Model Demonstrating Range of Possible Costs for Anemia Program Implementation

Category	Expenditure	Quantity	Cost/item	Items (low)	Total cost	Items (high)	Total cost
Laboratory	Laboratory assays	1	$47.26	300	$14,178.00	1000	$47,260.00
Personnel	Advanced practice provider	1	$74,000.00	300	$74,000.00	1000	$74,000.00
Facilities	Parking	3	$6.00	300	$5400.00	1000	$18,000.00
Medication	Intravenous iron	1	$300.00	60	$18,000.00	640	$192,000.00
				Total	$111,578.00	Total	$331,260.00

this patient population, Trentino et al[72] also conducted a retrospective cost analysis and reported that net hospital costs (revenue minus expenses) among patients for elective colorectal surgery were significantly less after implementation of a preoperative anemia clinic, iron screening, and IV iron management compared to controls.[73] They applied propensity matching techniques with multivariable regression models to adjust for differences in baseline characteristics between groups. They measured and compared units of RBCs transfused per admission which decreased 53% (142 vs 303 units per 1000 discharges; P = .006), and mean hospital length of stay which decreased 15% (7.7 vs 9.1 days; P = .008) in the screened and treated group. Forty-one percent of the screened patients received IV iron for anemia. The mean net hospital cost was $2629 lower in the group screened (P < .001).[72] In another retrospective study, elective orthopedic and gynecologic surgery patients treated through a preoperative anemia clinic compared to propensity matched controls demonstrated a significant reduction in RBC transfusion (12.6% vs 26.8%; P = .005) with a reduced LOS in the gynecologic surgery subgroup (2.2 vs 3.1 days; P = .002), although it did not include any cost analysis.[74]

In a recent retrospective observational study by Cahill et al.[39] among 240 patients evaluated before cardiac surgery, 22% were found to be anemic with 45 of 52 (87%) having iron deficiency and 7 (13%) having anemia without iron deficiency. The 2 most common treatments applied were IV iron ± folate (n = 36/45; 80%) and oral iron (n = 9/45; 20%). As compared to historical patients, study patients had significantly higher day-of-surgery Hb (10.6 ± 1.4 vs 9.8 1.3 g/dL; P < .001), lower utilization of RBC transfusion (0.86 ± 1.4 vs 2.78 ± 2.4; P < .001), fewer days in the ICU (2.1 ± 2.0 vs 4.0 ± 3.5; P = .002), and shorter total LOS (6.9 ± 4.8 vs 12.9 ± 6.8; P < .0001). Study patients also showed lower overall complication rates (P < .0001). Analysis of RBC acquisition cost and transfusion cost showed savings of 69% ($293 vs $945 and $656 vs $2116, respectively).

The predominance of preoperative anemia care coordination and management data are associated with decreased perioperative transfusion with inference to decreased cost of care. Therefore, we recommend the use of a preoperative anemia care coordination program as a cost-effective method to improve outcomes. Questions remain, however, regarding whether preoperative anemia care coordination and management portend a direct positive health economic impact.[75]

CONCLUSIONS

Anemia and iron deficiency are common in patients undergoing cardiac surgery and are associated with RBC transfusion. Accumulating evidence has led to strategies that clinicians can implement to address these important unmet needs. Notwithstanding the above, there is still a need for additional high-quality evidence to show that these best practices result in improved patient satisfaction and fewer complications.

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