 0003-4975/$36.00
Published by Elsevier Inc.
https://doi.org/10.1016/j.athoracsur.2021.03.033

PATIENT BLOOD MANAGEMENT GUIDELINES

STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management

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EXECUTIVE SUMMARY

Owing to the constantly evolving nature of the medical literature, The Society of Thoracic Surgeons (STS) clinical practice guidelines periodically undergo evaluation and updating. A multidisciplinary panel of experts was convened by STS, which includes members of the Society of Cardiovascular Anesthesiologists (SCA), the American Society of ExtraCorporeal Technology (AmSECT), and the Society for the Advancement of Blood Management (SABM), to review the latest data on patient blood management and to update the *2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines*.

The concept of patient blood management informs the recommendations in this document and stresses the importance of an evidence-based, multimodal, and multidisciplinary approach to not just conserving blood resources but also optimizing outcomes in patients at high risk for transfusion. The individual recommendations are meant to be conceived of as part of an all-inclusive protocol-based and shared decision-making approach rather than isolated interventions to reduce blood loss and transfusion.

Because standards for clinical practice guidelines have evolved since 2011, the authors were tasked with prioritizing topics for systematic review, while still aiming for the comprehensive approach of previous versions of this article. These high-priority topics make up the bulk of this article and resulted in 23 new or updated recommendations. Additionally, all previous recommendations not directly addressed were voted on by consensus and can be found in Table 1. Together, these recommendations address the full spectrum of care for patients undergoing cardiac surgery, as seen in Table 2.

Blood transfusion is a critical and life-saving facet of the care for cardiothoracic surgery patients. Inherent to the transfusing of blood is the understanding of the preservation of blood as well as the appropriateness of techniques to prevent hemorrhage through the clinical

Dr Stammers discloses a financial relationship with SpecialtyCare.

The Appendices can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2021.03.033] on https://www.annalsthoracicsurgery.org.

This article has been copublished in *The Annals of Thoracic Surgery*, the *Journal of ExtraCorporeal Technology*, and the *Journal of Cardiothoracic and Vascular Anesthesia*.

The Society of Thoracic Surgeons requests that this article be cited as: Tibi P, McClure RS, Huang J, et al. STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management. *Ann Thorac Surg.* 2021; https://doi.org/10.1016/j.athoracsur.2021.03.033.

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TABLE 1 Updated Recommendations From Previous Guidelines That Are Not a Focus of the Article

Intervention	ACC/AHA Class and Level
Preoperative identification of high-risk patients should be performed, and all available preoperative and perioperative measures of blood conservation should be undertaken in this group as they account for the majority of blood products transfused.	Class I, Level A
It is reasonable to discontinue low-intensity antiplatelet drugs (eg, aspirin) only in purely elective patients without acute coronary syndromes before operation with the expectation that blood transfusion will be reduced.	Class IIA, Level A
Minimization of phlebotomy through a reduction in blood sampling volumes and frequencies is a reasonable means of blood conservation.	Class IIA, Level B-NR (Nonrandomized)
The addition of a P2Y12 inhibitor to aspirin therapy, if indicated, in the immediate postoperative care of coronary artery bypass grafting patients prior to ensuring surgical hemostasis may increase bleeding and the need for surgical reexploration, and is not recommended until the risk of bleeding has abated.	Class III: No Benefit, Level C-LD (Limited Data)
Use of 1-deamino-8-D-arginine vasopressin (DDAVP) may be reasonable to attenuate excessive bleeding and transfusion in certain patients with demonstrable and specific platelet dysfunction known to respond to this agent (eg, uremic or CPB-induced platelet dysfunction, type I von Willebrand disease).	Class IIB, Level B-NR
Plasma transfusion is reasonable in patients with serious bleeding in the context of multiple or single coagulation factor deficiencies when safer fractionated products are not available.	Class IIA, Level B-NR
Prophylactic use of plasma in cardiac operations in the absence of coagulopathy is not indicated, does not reduce blood loss, and exposes patients to unnecessary risks and complications of allogeneic blood component transfusion.	Class III: Harm, Level A
When allogeneic blood transfusion is needed, it is reasonable to use leukoreduced donor blood, if available.	Class IIA, Level B-R (Randomized)
Use of recombinant factor VIIa concentrate may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB.	Class IIB, Level B-NR
Antithrombin III concentrates are indicated to reduce plasma transfusion in patients with antithrombin-mediated heparin resistance immediately before CPB.	Class I, Level A
In high-risk patients with known malignancy who require CPB, blood salvage using centrifugation of salvaged blood from the operative field may be considered when allogeneic transfusion is required.	Class IIB, Level B-NR
Centrifugation of pump-salvaged blood is reasonable for minimizing post-CPB allogeneic red blood cell transfusion.	Class IIA, Level A
Use of modified ultrafiltration may be reasonable for blood conservation and reducing postoperative blood loss in adult cardiac operations using CPB.	Class IIB, Level B-R
Routine use of red cell salvage using centrifugation is helpful for blood conservation in cardiac operations using CPB.	Class I, Level A
Direct reinfusion of shed mediastinal blood from postoperative chest tube drainage is not recommended as a means of blood conservation and may cause harm.	Class III: Harm, Level B-NR
A comprehensive multimodality blood conservation program led by a multidisciplinary team of health care providers should be part of any patient blood management program to limit utilization of blood resources and decrease the risk of bleeding.	Class I, Level B-R

ACC, American College of Cardiology; AHA, American Heart Association; CPB, cardiopulmonary bypass.

course. Although clinical practices have evolved through the centuries since Dr William Harvey discovered the circulation of blood in 1628 and attempted the first blood transfusion thereafter, there is significant variability in the practices of blood transfusion and conservation in all phases of the surgical care. In our current health care environment of value-based care, the need for practice guidelines must therefore be further emphasized. Additionally, the term "blood conservation" is yielding to a broader term "patient blood management" (PBM) that incorporates the need to not only "conserve" blood but, more importantly, to also take into account the assessment of the liquid organ, blood, as a vital entity in taking care of the surgical patient.

PBM is the broad implementation of many factors in a multidisciplinary fashion as opposed to just choosing isolated recommendations. The 4 major tenets of PBM are (1) managing anemia, (2) optimizing coagulation, (3) interdisciplinary blood conservation modalities, and (4) patient-centered decision making in order to achieve improved patient outcomes. Surgical outcomes are now being held to a higher standard, and sharing of outcomes, often in very public forums, is the new normal. Additionally, resource utilization and efficient care has to be foundational to our provision of care for every cardiothoracic surgery patient. High-value care with excellent outcomes by using the appropriate resources is now at the forefront of health care delivery.

This was a collective project of STS, SCA, AmSECT, and SABM to review the current literature, revise previous guidelines, and develop a series of practice guidelines that reflect the current evidence and practice portfolios that are used in cardiothoracic surgery in North America. Critical to this review and guideline development was an understanding of the patient care paradigm throughout the care continuum. The care continuum consisted of exploring the informed consent process, preoperative conditioning, the current clinical use of antiplatelet agents and preoperative anticoagulants, intraoperative blood management (including intravenous and topic hemostatic agent use), and the postoperative management of patients undergoing cardiopulmonary bypass (CPB). There are many stakeholders in the management of blood for patients throughout their clinical course, and therefore, we sought to include the evidence and practice of many

TABLE 2 All Current Recommendations for Patient Blood Management, Classified by Intervention Type and in Descending Order of Class of Recommendation and Level of Evidence

Intervention	ACC/AHA Class and Level
Preoperative interventions	
Preoperative identification of high-risk patients should be performed, and all available preoperative and perioperative measures of blood conservation should be undertaken in this group as they account for the majority of blood products transfused.	Class I, Level A
Assessment of anemia and determination of its etiology is appropriate in all patients undergoing cardiac surgery, and it is reasonable to treat with intravenous iron preparations if time permits.	Class IIA, Level B-R
In patients undergoing cardiac operations, it is reasonable to implement standardized transfusion protocols in order to reduce transfusion burden.	Class IIA, Level B-R
In patients who have (i) preoperative anemia, (ii) refuse blood transfusion, (iii) or are deemed high-risk for postoperative anemia, it is reasonable to administer preoperative erythropoietin-stimulating agents and iron supplementation several days prior to cardiac operations to increase red cell mass.	Class IIA Level B-R
Minimization of phlebotomy by reduced volume and frequency of blood sampling is a reasonable means of blood conservation.	Class IIA, Level B-NR
Preoperative treatment of asymptomatic anemia and thrombocytopenia with transfusion is of uncertain benefit.	Class III: No Benefit, Level B-NR
Preoperative antiplatelet management	
In order to reduce bleeding in patients requiring elective cardiac surgery, ticagrelor should be withdrawn preoperatively for a minimum of 3 days, clopidogrel for 5 days, and prasugrel for 7 days.	Class I, Level B-NR
It is reasonable to discontinue low-intensity antiplatelet drugs (eg, aspirin) only in purely elective patients without acute coronary syndromes before operation with the expectation that blood transfusion will be reduced.	Class IIA, Level A
Laboratory and/or point-of-care measurement of antiplatelet drug effect in patients having received recent dual-antiplatelet therapy can be useful to assess bleeding risk or to guide timing of surgery.	Class IIA, Level B-R
The addition of a P2Y12 inhibitor to aspirin therapy, if indicated, in the immediate postoperative care of coronary artery bypass grafting patients prior to ensuring surgical hemostasis may increase bleeding and the need for surgical reexploration and is not recommended until the risk of bleeding has abated.	Class III: No Benefit, Level C-LD
Preoperative anticoagulants	
In patients in need of emergent cardiac surgery with recent ingestion of a nonvitamin K oral anticoagulant (NOAC) or laboratory evidence of a NOAC effect, administration of the reversal antidote specific to that NOAC is recommended (ie, administer idarucizumab for dabigatran at appropriate dose or administer andexanet-α for either apixaban or rivaroxaban at appropriate dose).	Class IIA, Level C-LD
If the antidote for the specified NOAC is not available, prothrombin concentrate is recommended, recognizing that the effective response may be variable.	Class IIA, Level C-LD
Pharmacologic agents	
Use of synthetic antifibrinolytic agents such as epsilon-aminocaproic acid (EACA) or tranexamic acid reduce blood loss and blood transfusion during cardiac procedures and are indicated for blood conservation.	Class I, Level A
Tranexamic acid reduces bleeding and total transfusion during off pump coronary artery bypass graft surgery.	Class IIA, Level B-R
Topical application of antifibrinolytic agents to the surgical site after cardiopulmonary bypass (CPB) is reasonable to limit chest tube drainage and transfusion requirements after cardiac operations using CPB.	Class IIA, Level B-R
Use of 1-deamino-8-D-arginine vasopressin (DDAVP) may be reasonable to attenuate excessive bleeding and transfusion in certain patients with demonstrable and specific platelet dysfunction known to respond to this agent (eg, uremic or CPB-induced platelet dysfunction, type I von Willebrand disease).	Class IIB, Level B-NR
Blood products and derivatives	
Antithrombin III concentrates are indicated to reduce plasma transfusion in patients with antithrombin mediated heparin resistance immediately before cardiopulmonary bypass.	Class I, Level A
When allogeneic blood transfusion is needed, it is reasonable to use leukoreduced donor blood, if available.	Class IIA, Level B-R
Plasma transfusion is reasonable in patients with serious bleeding in the context of multiple or single coagulation factor deficiencies when safer fractionated products are not available.	Class IIA, Level B-NR
Prothrombin concentrate is reasonable to consider over fresh frozen plasma as first-line therapy for refractory coagulopathy in cardiac surgery in select situations to reduce bleeding.	Class IIA, Level B-NR
Use of recombinant factor VIIa concentrate may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB.	Class IIB, Level B-NR
Prophylactic use of plasma in cardiac operations in the absence of coagulopathy is not indicated, does not reduce blood loss, and exposes patients to unnecessary risks and complications of allogeneic blood component transfusion.	Class III: Harm, Level A
Perfusion interventions	
Retrograde autologous priming of the CPB circuit should be used wherever possible.	Class I, Level B-R
Reduced priming volume in the CPB circuit reduces hemodilution and is indicated for blood conservation,	Class I, Level B-NR
Acute normovolemic hemodilution (ANH) is a reasonable method to reduce bleeding and transfusion.	Class IIA, Level A
Minimally invasive extracorporeal circulation is reasonable to reduce blood loss and red cell transfusion as part of a combined blood conservation approach.	Class IIA, Level B-R
Use of modified ultrafiltration may be reasonable for blood conservation and reducing postoperative blood loss in adult cardiac operations using CPB.	Class IIB, Level B-R

(*Continued*)

TABLE 2 Continued

Intervention	ACC/AHA Class and Level
Blood salvage interventions	
Routine use of red cell salvage using centrifugation is helpful for blood conservation in cardiac operations using CPB.	Class I, Level A
Centrifugation of pump-salvaged blood is reasonable for minimizing post-CPB allogeneic red blood cell transfusion.	Class IIA, Level A
In high-risk patients with known malignancy who require CPB, blood salvage using centrifugation of salvaged blood from the operative field may be considered when allogeneic transfusion is required.	Class IIB, Level B-NR
Direct reinfusion of shed mediastinal blood from postoperative chest tube drainage is not recommended as a means of blood conservation and may cause harm.	Class III: Harm, Level B-NR
Postoperative fluid management	
It is reasonable to administer human albumin after cardiac surgery to provide intravascular volume replacement and minimize the need for transfusion.	Class IIA, Level B-R
Hydroxyethyl starch is not recommended as a volume expander in CPB patients as it may increase the risk of bleeding.	Class III: No Benefit, B-R
Transfusion algorithms	
In patients undergoing cardiac surgery, a restrictive perioperative allogeneic red blood cell (RBC) transfusion strategy is recommended in preference to a liberal transfusion strategy for perioperative blood conservation, as it reduces both transfusion rate and units of allogeneic RBCs without increased risk for mortality or morbidity.	Class I, Level A
Goal directed transfusion algorithms which incorporate point of care testing, such as with viscoelastic devices, are recommended to reduce periprocedural bleeding and transfusion in cardiac surgical patients.	Class I, Level B-R
Allogeneic RBC transfusion is unlikely to improve oxygen transport when the hemoglobin concentration is greater than 10 g/dL and is not recommended.	Class III: No Benefit: Level B-R
Management of blood resources	
A comprehensive multimodality blood conservation program led by a multidisciplinary team of health care providers should be part of any patient blood management program to limit utilization of blood resources and decrease the risk of bleeding.	Class I, Level B-R

ACC, American College of Cardiology; AHA, American Heart Association.

different groups and experts. Ultimately, we sought to provide a comprehensive set of guidelines that are practical and will be received as being reasonable and well-researched. While we have collectively tried to accumulate the evidence and data from a broad number of stakeholders and sources, we recognize that it may be impossible to have every data point. Our intent is to present the most comprehensive set of guidelines possible, and we hope that this will serve as a resource so to improve the outcomes of patients undergoing cardiothoracic surgery.

METHODOLOGY

The STS Workforce on Evidence-Based Surgery assembled a Task Force in 2018 to update the 2011 STS/SCA Blood Conservation Clinical Practice Guidelines, seeking representatives again from SCA as well as AmSECT and SABM.

The members of the writing committee submitted conflict of interest disclosure forms, which were reviewed by the Chair and STS staff before confirmation for potential conflicts from relevant relationships with industry.

The writing committee reviewed the topics covered by the 2011 Guidelines and developed 11 questions in the Population, Intervention, Comparator, and Outcomes format (PICO) intended to focus on the highest priority and most clinically impactful areas for a systematic review. The PICO questions were sent to a research librarian in March 2018 to develop a strategy to identify relevant articles published in English since 2009, the most recent year of data included in the previous guidelines. Strategies were developed for both MEDLINE and Embase, the details for which may be found in Appendix 1. Reference lists were manually scanned for additional relevant results. This strategy resulted in 1227 potentially relevant abstracts, which were screened by a group of authors (S.F., K.K., R.S.M., D.C.). A total of 87 articles met the inclusion criteria. The primary reasons for exclusion were if the population was not relevant (eg, patients undergoing percutaneous coronary intervention [PCI] or another type of surgery aside from cardiac) or the primary outcomes were secondary markers with an uncertain relationship to the hard clinical outcomes selected by the writing committee.

Two authors (S.F., K.K.) developed an evidence table of the relevant papers (Appendix 2) and rated the studies for risk of bias. The Newcastle-Ottawa scale was used for observational studies (Appendix 3), and a custom-made checklist was used for randomized control trials (RCTs) and meta-analyses (Appendix 4). The bulk of the article is focused on the results of this systematic review. Recommendations from previous versions of this article were assessed by an electronic survey circulated to the authors to determine their current relevance. A full account of the evolution of the recommendations on this topic is in Appendix 5, which shows that many previous recommendations were retired for lack of current clinical relevance, having outdated techniques, or lack of improvement in the evidence for the weaker statements.

Recommendations that are not a focus of this updated article, but which were maintained in this version due to having continued clinical relevance, are included in Table 1. All current and valid recommendations are categorized and presented in Table 2. Voting on recommendations used a modified Delphi method of 3 rounds of voting to reach consensus, in which responses were required by 80% of the authors, with 75% agreement on class and level of evidence as defined by the American College of Cardiology (ACC)/American Heart Association (AHA) Classification System (Appendix 6).

The resulting article was reviewed by the STS Workforce on Evidence-Based Surgery, the STS Council Operating Board on Quality, Research, and Patient Safety, and the Executive Committee, along with a 2-week member comment period available to members of every participating society. The Board of Directors of the SCA and AmSECT also reviewed the document before publication.

These guidelines were developed by the participating societies without commercial support and will be reviewed for a potential update within 5 years of publication.

PREOPERATIVE MANAGEMENT

RISK ASSESSMENT FOR TREATMENT OF ANEMIA

- **Assessment of anemia and determination of its etiology is appropriate in all patients undergoing cardiac surgery, and it is reasonable to treat with intravenous iron preparations if time permits. (Class IIA, Level B-R)**

It is well known from the original 2007 STS Blood Conservation Guidelines that preoperative preparation of patients with regard to blood use in cardiac surgery, when feasible, is of the utmost importance for consistent blood conservation strategies. Identification of high-risk individuals, whether it be from advanced age, preoperative anemia, or abnormal coagulation profiles, is a Class 1 intervention. Additionally, one of the most significant determinants of patients needing perioperative transfusions is preoperative anemia. Anemia is extremely prevalent in the cardiac surgical population, especially in elderly patients or patients with multiple comorbidities and chronic diseases. Recent studies identify the prevalence of anemia in the 30% to 40% range[1,2] and severe anemia by World Health Organization classification of hemoglobin of less than 8 g/dL in the 8% to 10% range.[3]

Iron deficiency is the most prevalent cause of anemia in the cardiac surgical population, occurring in up to 50% of anemic patients.[4] Patients with preoperative anemia are more likely to require transfusions, and it is obvious that if the ability to treat iron-deficiency anemia is available without any untoward effects, it should be instituted before surgery. Differentiation must be made between anemias caused by iron deficiency as opposed to other causes of anemia. Iron-deficiency anemia is usually microcytic, whereas normocytic or macrocytic anemia stem from a variety of causes. Routine iron studies are of importance in the determination of the type of anemia present and should be done routinely in the careful preoperative assessment of patients so that treatment can be instituted if warranted.

There is a distinct correlation between preoperative anemia and worse clinical outcomes in most studies. Usually, the greater the anemia, the more severe the complications. In a prospective observational study of more than 200 patients undergoing coronary artery bypass graft (CABG) surgery, preoperative hematocrit remained an independent predictor for major morbidity (odds ratio [OR], 0.95; $P = .01$), while transfusion was also a strong predictor (OR, 4.86; $P < .001$).[5] Multiple recent retrospective studies demonstrate higher morbidity and mortality in patients with preoperative anemia, although some only show an association with long-term mortality. Additionally, there appears to be a cumulative effect of anemia and transfusions that increases risks.

In comparisons of patients undergoing CABG surgery who did or did not receive a transfusion, there was greater mortality in the patients who received a transfusion (11% vs 5.3%; $P = .001$). Patients with anemia who received a transfusion had a hazard rate for mortality 3-times higher than nonanemic patients who did not receive transfusion (hazard ratio [HR], 2.918; 95% confidence interval [CI], 1.512-5.633; $P = .001$), and twice that of anemic patients who did not receive a transfusion (HR, 2.087; 95% CI, 1.004-4.336; $P = .049$).[6] Preoperative anemia has also been associated with increased transfusion rates and longer intensive care unit (ICU) and hospital lengths of stay[1] and an increase in acute kidney injury.[7] However, 1 retrospective study found only normocytic or macrocytic anemia was associated with increased adverse events.[8]

PREOPERATIVE TREATMENT OF ANEMIA—PHARMACOLOGIC AGENTS

- **In patients who have (i) preoperative anemia, (ii) refuse blood transfusion, (iii) or are deemed high-risk for postoperative anemia, it is reasonable to administer preoperative erythropoietin stimulating agents (ESA) and iron supplementation several days prior to cardiac operations to increase red cell mass. (Class IIA, Level B-R)**

Among the difficulties in treatment of the anemic patient is the oftentimes lack of a safe waiting period, the “gentle” insistence by referring physicians for more urgent treatment than is necessary, the inconvenience,

cost, and/or refusal to pay for iron and EPO therapy by insurers and the oftentimes overstated risks of these therapies. Nevertheless, treatment of an anemic patient before surgery is an appropriate preoperative intervention and should be considered as part of any patient's careful workup and preparation for cardiac surgery, if time permits.

The treatment of anemia before heart surgery has been significantly studied, but almost all trials combine treatment of iron deficiency with both iron preparations *and* erythropoietin (EPO). Many of these studies, although not all, show increases in hemoglobin levels and reductions in transfusions. There is a paucity of studies that treat preoperative iron-deficiency anemia with just iron. One prospective observational study demonstrated an increased hemoglobin level in pretreated anemic patients,[9] but a small RCT of only 50 patients did not.[10] Therefore, it is difficult to confidently state that the direct treatment of iron-deficiency anemia before cardiac surgery with iron alone will result in improved outcomes, but it is clear that the treatment of anemia is warranted in the elective surgical patient. Patients should undergo careful preoperative testing to rule out absolute or functional iron deficiency and be treated accordingly if possible. EPO therapy, if begun a few days preoperatively, may reduce adverse outcomes by augmenting red cell mass in anemic patients treated with iron. A small RCT by Yoo and colleagues[11] using a regimen of erythropoietin-stimulating agents (ESAs) and intravenous iron showed significant improvements in units of transfusion (1.0 ± 1.1 units vs 3.3 ± 2.2 units in the control group; $P = .001$). Likewise, a prospective observational study by Cladellas and colleagues[12] of ESAs and iron showed a reduction in the rate of patients who received a transfusion (67% vs 93% in the control group; $P < .001$) and 30-day mortality (multivariable OR, 0.16; 95% CI, 0.28-0.97; $P = .04$).

There is enough evidence to state that the nonanemic patient will do better with surgery than the anemic patient and undoubtedly be less at risk for transfusions with its known risks for adverse effects. Unfortunately, oral iron therapy is poorly tolerated by many patients, is oftentimes not very effective, and the course of treatment is too lengthy for most cardiac surgical patients. There are numerous intravenous iron preparations with differences in dosage recommendations that are very effective even for 1 to 2 weeks.

Recombinant human EPO is commercially available in multiple forms to treat anemia, especially in patients with renal insufficiency and failure. Concerns have been raised in the past regarding a potential increased incidence of cardiovascular events and mortality; however, more recent studies have failed to corroborate these findings, reporting no adverse effects of short-term ESA pretreatment with or without concomitant iron of anemic patients.[13,14] Additionally, several RCTs have shown a nephroprotective effect of preoperative treatment on anemic patients with ESAs only.[15-17]

Other considerations for the use of ESAs include situations in which endogenous EPO production is limited. For instance, β-blockers suppress endogenous EPO production,[18] and perioperative anemia decreases the cardioprotective effect of β-blockade.[19] Additionally, cytokines stimulated by the inflammatory response associated with CPB limit production of EPO.[20] Perioperative renal ischemia may limit the production of EPO. Likewise, careful postoperative management may improve tissue oxygen delivery and suppress endogenous EPO production despite postoperative anemia. Decreased perioperative EPO production favors a short preoperative course of ESA (a few days before the operation) to treat reduced red blood cell (RBC) volume in selected individual patients.

In a prospective RCT of 600 anemic patients, a single dose of 80,000 units of epoetin-α given to patients 2 days before surgery resulted in significantly lower postoperative transfusion rates (17% vs 39%; risk ratio [RR], 0.436; $P < .0005$) and higher hemoglobin on day 4 after surgery (10.2% vs 8.7%; $P < .0005$), although no significant differences in mortality and adverse events at 45 days.[21] A second randomized trial of 320 patients who underwent a variety of cardiac procedures off-pump also resulted in fewer RBC transfusions (37.1% vs 16.1%; RR, 0.425; $P = .007$), without a significant difference in adverse events, although this study required 4 times as many patients to detect such a difference.[22] The study group in this trial received multiple subcutaneous doses starting on preoperative day 2 and continuing to postoperative day 2. A review and meta-analysis of perioperative ESA administration suggested a cytoprotective effect on various organs, specifically the heart and kidneys. This effect is more strongly associated with preoperative vs perioperative EPO and patients at lower risk for cardiac surgery-associated acute kidney injury.[23]

It has been suggested that a short-term combination therapy with intravenous iron, subcutaneous EPO-α, vitamin B_{12}, and oral folic acid may provide reduced risk of transfusion in anemic patients undergoing cardiac procedures.[24] This observation needs further investigation before broad-based acceptance can be recommended.

The safety and efficacy of additional pharmacologic therapies, such as vitamin K and levosimendan to reduce bleeding, have also been investigated in recent years, although the data are too preliminary for this guideline document.

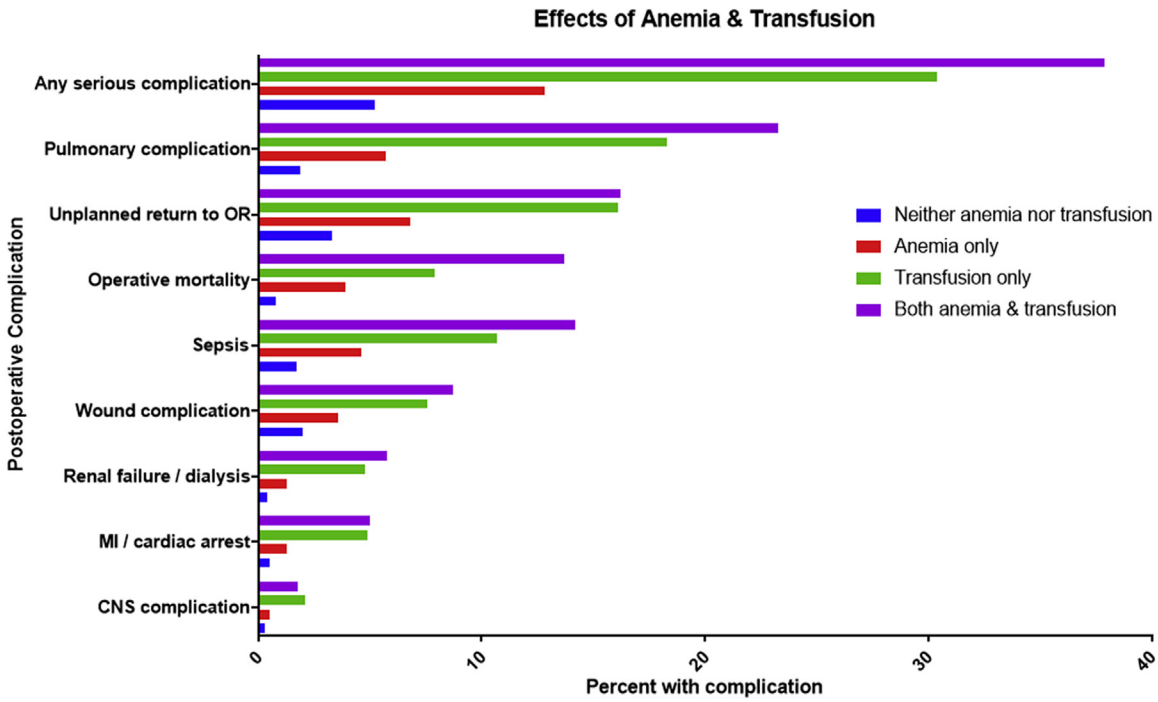

FIGURE 1 Increased association of adverse outcomes in patients with anemia and/or transfusion. (CNS, central nervous system; MI, myocardial infarction; OR, operating room.) (Reproduced from Ferraris and colleagues[27] with permission from Elsevier.)

PREOPERATIVE DIAGNOSIS AND TREATMENT OF ANEMIA—NONPHARMACOLOGIC INTERVENTIONS

- **In patients undergoing cardiac operations, it is reasonable to implement standardized transfusion protocols in order to reduce transfusion burden. (Class IIA, Level B-R)**
- **Preoperative treatment of asymptomatic anemia and thrombocytopenia with transfusion is of uncertain benefit. (Class III: No Benefit, Level B-NR)**

Significant dilutional anemia as a result of CPB occurs in patients with borderline preoperative hemoglobin concentrations. Importantly, preoperative and intraoperative correction of anemia with RBC transfusion has not been demonstrated to mitigate the risks of end-organ dysfunction. Preventing dilutional anemia and avoiding transfusion in CPB operations are supported as the most effective means of preserving end-organ function.[25]

The interplay of anemia and transfusion is complex, especially in the perioperative setting where multiple components of the hemostatic mechanism are required for control of bleeding and for optimal outcomes[26] (Figure 1[27]). Preoperative anemia, especially in the absence of preoperative transfusions or other treatments, seems to be a risk factor for morbidity and mortality after cardiac operations,[10,28,29] but there is conflicting evidence that preoperative transfusion to higher hemoglobin levels impacted this risk.[28,30,31] Similarly, chronic thrombocytopenia is a risk for adverse outcomes after cardiac interventions, and the benefit of prophylactic preoperative transfusion of platelets in this setting is uncertain.[32]

Consensus favors robust blood conservation before, during, and after cardiac operations. The role of preoperative prophylactic transfusion is uncertain, although probably not helpful.

Use of preoperative autologous blood donation (PABD) is a theoretically rational approach for patients undergoing elective cardiac procedures using CPB. While there has been a slight uptick in the number of autologous blood donations in recent years (2015-2017), it still remains a fraction (<1%) of total collected RBCs.[33] This result is partially due to the waning public perception of risks associated with allogenic blood transfusions and the declining demand due to the proliferation of blood management programs.[34]

There is a need for further study of the relative effectiveness of PABD in cardiac surgery. In a 2010 propensity-matched observational study of 432 patients at a single center in Germany, PABD was associated with a lower rate of RBC and fresh frozen plasma (FFP) transfusion without additional transfusion-related adverse effects.[35] However, a recent analysis showed

TABLE 3 Variability in Blood Products and Procedure Acceptance Among Jehovah's Witnesses

Not Acceptable	May Be Acceptable
Blood, blood components, and blood fractions	
Whole blood	Recombinant products such as G-CSF, EPO
Red cells	Albumin
White cells	Clotting factors
Platelets	Colony-stimulating factors
Fresh frozen plasma	Cryoprecipitate
Autologous predonation	Hemoglobin-based oxygen carriers
	Fibrinogen/fibrin
	Immunoglobulins
	Interferon/interleukin
	Thrombin/prothrombin
	Rh factor
	Sealants
Therapeutic procedures involving patient's own blood	
Autologous predonation and reinfusion	Cell salvage
	ANH/hemodilution
	Extracorporeal blood recirculation
	Hemodialysis
	Blood patch
	Apheresis/plasmapheresis
	Platelet gel-autologous
	Cell labeling or tagging

ANH, acute normovolemic hemodilution; EPO, erythropoietin; GCSF, granulocyte colony-stimulating factor.

that PABD in the setting of strict policies for blood conservation was ineffective in reducing allogeneic blood transfusion for young and relatively healthy patients who underwent minimally invasive cardiac surgery. Although the PABD group had higher postoperative hemoglobin levels, there was no clear clinical benefit in the early postoperative period, despite a great deal of effort and additional cost. These results suggest that PABD is neither a uniformly cost-effective nor a definitively beneficial intervention in patients undergoing minimally invasive cardiac surgery.[36] There are currently insufficient data to make a definitive recommendation on the practice of PABD in cardiac surgery.

There is good observational data to suggest that a standardized protocol for evidence-based blood product transfusion and blood conservation in the perioperative setting favors improved clinical outcomes in routine cardiac procedures. A propensity-matched analysis suggested that a comprehensive blood conservation protocol centering on acute normovolemic hemodilution (ANH) and including routine use of antifibrinolytics, topical hemostatic agents, and strict transfusion triggers was associated with reductions in any complication (29.5% vs 18.8%; $P = .007$), fewer postoperative transfusions (70.1% vs 50.9%; $P < .001$), and a lower transfusion volume (1.82 vs 1.21 units; $P = .002$) without any associated change in mortality.[37]

INFORMED CONSENT AND PREOPERATIVE INTERVENTIONS FOR PATIENTS REFUSING BLOOD PRODUCTS. The right of a competent adult to make an informed decision regarding recommended therapeutic procedures is a basic, well-established legal requirement.[38,39] These rights are rooted in the fundamental principles of clinical/legal ethics: autonomy, veracity, beneficence, nonmaleficence, and justice.[40]

Designation of decision-making capacity at a certain age is an arbitrary but necessary legal distinction. In the case of unemancipated patients aged younger than 18 years, family members (and patients) cannot generally refuse treatment deemed to be life-saving. In the emergency setting when the minor's life is at risk, it may be acceptable to administer a transfusion to an unemancipated patient who is aged younger than 18 years over the objections of parents or patient. In cases where a transfusion is deemed medically necessary for a minor patient and the child's life is in danger, courts will typically intervene over the religious objections of the parents and the patient.[41] In a nonemergency setting, surgeons may seek to obtain a court appointed guardian for permission for transfusion.

To provide optimal care for adult autonomous patients who are Jehovah's Witnesses, surgeons should aim to respect and accommodate each patient's values and target the best possible outcome given the patient's desires and his or her clinical condition. Jehovah's Witnesses refuse certain aspects of hemotherapy. Proscribed blood components are red cells, leukocytes, platelets, and plasma. In general the remaining hemotherapies are left to the conscience of the individual Witness to decide.[42,43] See Table 3 for a summary of blood products that may or may not be acceptable to Jehovah's Witnesses.

In the nonemergent setting, acceptable treatment strategies should be explored with the patient as early as possible in the course of preoperative planning. Optimally, time should be allowed for patients to reflect on what they have learned and to have the opportunity to ask questions, receive clarification, and make an informed decision. Even in emergent situations, best efforts should be put forward to use the elements of informed consent with the patient or his or her appointed health care agent.

Admittedly, PBM should be practiced in all patients regardless of their personal beliefs. Nevertheless, there are multiple nuances that must be considered and specifically addressed in Jehovah's Witnesses such as the consensual use of cell salvage, ANH, and other modalities. The consent process requires these issues to be

discussed and agreed upon and, bear in mind, informed consent implies the ability to give informed choice.[44]

PREOPERATIVE ANTICOAGULANTS

- **In patients in need of emergent cardiac surgery with recent ingestion of a nonvitamin K oral anticoagulant (NOAC) or laboratory evidence of a NOAC effect, administration of the reversal antidote specific to that NOAC is recommended (ie, administer idarucizumab for dabigatran at the appropriate dose or administer andexanet-α for either apixaban or rivaroxaban at the appropriate dose). (Class IIA, Level C-LD)**
- **If the antidote for the specified NOAC is not available, prothrombin concentrate is recommended, recognizing that the effective response may be variable. (Class IIA, Level C-LD)**
- **Prothrombin concentrate is reasonable to consider over fresh frozen plasma as first-line therapy for refractory coagulopathy in cardiac surgery in select situations to reduce bleeding. (Class IIA, Level B-R)**

Most aspects of the contemporary anticoagulation management strategies in the preoperative preparatory phase for cardiac surgical patients (to minimize bleeding risk) are reflective of the same guiding principles put forth in the 2011 Blood Conservation Practice Guidelines. Having said this, NOACs are a new subgroup of pharmacologic agents with widespread use since the 2011 guidelines,[45,46] about which the cardiac surgical teams need to be knowledgeable, because they may portend increased bleeding if not managed properly. The NOACs—dabigatran (thrombin inhibitor), apixaban, betrixaban, edoxaban, and rivaroxaban (factor Xa inhibitors)—are proven better alternatives to the vitamin K antagonist, warfarin, for stroke prevention in nonvalvular atrial fibrillation as well as to treat venous thromboembolism.[47-50] Moreover, the pharmacologic properties of NOACs confer increased convenience to patients through fixed dosing and the elimination of routine monitoring. Many patients in need of cardiac surgery use these medications.

Despite their advantages, NOACs present some periprocedural challenges for operations with a high-risk bleeding profile. Available measurement assays to assess anticoagulation for NOACs are imprecise, and the availability of reversal agents is limited.[51-53] Given the predictable and rather short half-life to NOACs, in the elective setting, discontinuation for at least 2 days before surgery is recommended, although renal impairment will require extending this discontinuation for additional days in select situations.[54,55] Literature is limited, yet 2 recent retrospective studies confirm increased bleeding complications in the face of preoperative NOAC therapy, with 1 of the studies advocating for the consideration of longer discontinuation periods before elective cardiac surgery.[56,57]

A prior concern with NOACs was the limited availability of reversal agents. Going forward this will be less of a concern because the United States Food and Drug Administration has recently approved antidotes for the more widely used NOACs. For dabigatran, idarucizumab, a human monoclonal anti-dabigatran antibody is now available. For apixaban and rivaroxaban, the modified recombinant factor Xa, andexanet-α, is available.[58] In situations where these antidotes are not readily available, prothrombin complex concentrates (PCCs) may prove beneficial and are recommended, although efficacy may vary.[55] As well, although not widely available, point-of-care (POC) testing with thrombin clotting time for dabigatran or anti-factor Xa assays for apixaban and rivaroxaban can aid in determining the anticoagulant effect of these NOACs at the time of emergent surgery.[51-53] The use of these laboratory tests is recommended if readily available.

Beyond being a nonspecific antidote to NOACs in emergent situations, the safety and effectiveness of PCC to reduce bleeding in cardiac surgery has been further evaluated since the 2011 guidelines. Already the preferred therapy for emergent warfarin reversal,[59] PCC may also be applicable in cases of refractory bleeding.[60] PCC facilitate rapid correction of vitamin K-dependent coagulation factors without the potential deleterious effects of volume overload attributed to FFP. Still, the literature to evaluate PCC use in such situations remains limited, and theoretical concerns around adverse thrombogenicity have yet to be elucidated. A study that included 2 analyses: a propensity score-adjusted multivariate analysis of 971 patients, and propensity score-matched cohorts of 225 pairs using PCC or FFP for first-line therapy in coagulopathy showed a decrease in postoperative blood loss and blood transfusions. However, in the multivariate analysis, this was at the expense of increased acute kidney injury and renal replacement therapy. These differences were not confirmed in the analysis of the matched pairs.[61] There was no difference in thromboembolic events.

A meta-analysis of observational studies with 861 patients, including those in the aforementioned propensity-matched analysis, also showed decreased postoperative blood loss and blood transfusions with PCC at varying doses. There was no difference in thromboembolic events and no difference in acute kidney injury. Noteworthy, there was a nonsignificant trend toward increased renal replacement therapy in the pooled outcome, although the relatively wide 95% CI suggests a fair amount of uncertainty (OR, 0.41; 95% CI, 0.16-1.02; $P = .06$). Hospital mortality and reexploration were likewise not statistically significant.[62]

A moderate level of evidence suggests that PCC is more effective than FFP for refractory coagulopathy in cardiac surgery. The associated risks are likely acceptable in many situations, but further evidence is required to fully delineate the risk benefit ratio.

ANTIPLATELETS

- **In order to reduce bleeding in patients requiring elective cardiac surgery, ticagrelor should be withdrawn preoperatively for a minimum of 3 days, clopidogrel for 5 days, and prasugrel for 7 days. (Class I, Level B-NR)**
- **Laboratory and/or point-of-care measurement of antiplatelet drug effect in patients having received recent dual-antiplatelet therapy can be useful to assess bleeding risk or to guide timing of surgery. (Class IIA, Level B-R)**

Dual-antiplatelet therapy (DAPT) with a P2Y12 inhibitor and aspirin is well-demonstrated to decrease ischemic risk and thrombotic complications in patients with acute coronary syndromes (ACS) and after PCI compared with single-antiplatelet therapy (SAPT) with aspirin alone.[63-67] However, a percentage of ACS and/or PCI patients will still require surgical coronary revascularization, and multiple randomized clinical trials, observational studies, and meta-analyses have demonstrated that maintenance of DAPT up to the time of cardiac surgery (eg, CABG) increases intraoperative and perioperative bleeding, rates of transfusion of blood and blood products (especially platelets), and postoperative reexploration for mediastinal bleeding.[68-74] Thus, for ACS patients requiring surgical intervention, where feasible, preoperative cessation of the P2Y12 inhibitor has been recommended in previous American and European guidelines.[59,75,76]

In patients in whom preoperative cessation of P2Y12 inhibitor is not possible, many observational studies suggest that preoperative assessment of antiplatelet drug activity is important in assessing bleeding risk, with additional randomized data available on the effectiveness of whole-blood impedance aggregometry tests.[77,78] The results of POC platelet function testing correlate well with bleeding after cardiac surgery, with higher levels of platelet inhibition predicting increased bleeding and transfusions. When preoperative POC platelet function testing is used in the elective surgery patient, a significant platelet inhibitory test result may lead to surgical postponement, which can lower the risk of bleeding to that of a patient who was not exposed to platelet-inhibiting drugs. POC platelet function testing in patients whose surgery cannot be postponed is also useful in predicting the extent of platelet inhibition and the risk of bleeding.

The most commonly used P2Y12 inhibitors in the setting of ACS and PCI have been clopidogrel, prasugrel, and ticagrelor. Each of these agents exhibits different pharmacokinetic and pharmacodynamic properties[79] as well as interindividual variability in antiplatelet effect. Thus, the optimal minimum time frame(s) in which preoperative discontinuation of the different P2Y12 inhibitors (with continuation of aspirin) resulted in no increased perioperative bleeding, and whether preoperative withdrawal of the P2Y12 inhibitor also translates to other adverse outcomes, has been the subject of numerous investigations. As of the time of this writing, the preponderance of the data demonstrates that bleeding risk is not elevated when ticagrelor has been withdrawn for a minimum of 3 days, clopidogrel for 5 days, and prasugrel for 7 days preoperatively, as discussed more specifically subsequently. Further, laboratory and/or POC measurement of residual platelet reactivity in a given individual while on treatment or after withdrawal can be useful to guide the timing of elective surgical intervention.

Clopidogrel. The well-described interindividual variability of actual platelet inhibition from clopidogrel due to polymorphisms of CYP enzyme metabolism in some individuals resulting in their "non- or poor-responder status" notwithstanding, data suggesting at least a 5-day washout of clopidogrel before elective cardiac surgery comes primarily from studies conducted between 2004 and 2019.

The 2009 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction and ACC/AHA/Society for Cardiovascular Angiography and Interventions Guidelines on Percutaneous Coronary Intervention recommended the withdrawal of clopidogrel for at least 5 days before CABG with only a level of evidence "C" (expert consensus opinion). However, a 2014 meta-analysis by Cao and colleagues[80] of 5 studies from 2004 to 2009 compared the impact of less or more than 5 days of clopidogrel washout on perioperative bleeding, mortality, and morbidity in 2632 patients from a larger cohort of 6385 for other analyses in the 5 studies. Patients who had more than 5 days of washout demonstrated a lower incidence of major bleeding (19.7% vs 30.2%; $P = .04$), decreased need for reoperation (1.8% vs 3.2%; $P = .03$), and a lower incidence of the composite end point that included mortality and myocardial infarction, recurrent ischemia, stroke, and emergency revascularization (7.9% vs 9.7%; $P = .01$) by comparison with those with less than 5 days of washout. No statistical significance was demonstrated in the all-cause mortality rates between the 2 treatment groups (3.1% vs 4.0%; $P = .61$).

More recently, in a 2016 retrospective analysis of prospectively collected data of 2244 ACS DAPT patients who underwent urgent or elective CABG, Hansson and colleagues[71] demonstrated that discontinuation of clopidogrel 3 to 5 days before surgery resulted in a higher

rate of major bleeding complications compared with discontinuation greater than 5 days preoperatively (unadjusted OR, 1.71; 95% CI, 1.04-2.79; $P = .033$).

As well, Tomsic and colleagues[72] demonstrated in their 2016 retrospective observational cohort study of 626 patients on DAPT presenting for isolated on-pump CABG that the subgroup of patients with clopidogrel withdrawn less than 5 days before elective cardiac surgery had higher transfusion needs (71.2% vs 41.3%; $P < .001$), need for multiple transfusions (14.4% vs 3.7%; $P < .001$), and a higher incidence of mediastinal chest tube drainage of 1000 mL in the first 12 hours postoperatively (26.4% vs 12.6%; $P < .001$) compared with those who remained only on aspirin.[72] A trend was demonstrated toward the increased need for surgical reexploration between those with clopidogrel withdrawn for less than 5 days and the aspirin-only group, but this did not attain statistical significance (10.4% vs 5.4%; $P = .051$).

Ticagrelor. Ticagrelor is an oral direct-acting, competitive P2Y12 inhibitor that, compared with clopidogrel, exhibits a faster onset and offset of effect, and more consistent inhibition of platelet function among individuals because it does not require metabolic activation.[79,81]

Although it was appreciated that continuation of DAPT to the time of surgery would result in excessive bleeding, which had been associated with increased mortality, there was also concern that delays of CABG while awaiting P2Y12 washout to reduce bleeding risk may increase the risk of myocardial injury and/or stent thrombosis while awaiting surgery.[65]

Given the known "fast offset" time of ticagrelor, subgroup analyses results from the Platelet Inhibition and Patient Outcomes (PLATO) trial suggested that discontinuation of ticagrelor 2 to 3 days preoperatively should be sufficient to balance the concomitant risks of perioperative bleeding and thrombotic events,[69] but subsequent studies demonstrated that at least 3 days of ticagrelor washout minimizes bleeding risk without apparently increasing the risk of thrombotic events.

Tomsic and colleagues[72] demonstrated in their 2016 retrospective observational cohort study of 626 patients on DAPT presenting for isolated on-pump CABG that the subgroup of patients with ticagrelor withdrawn less than 72 hours preoperatively had higher transfusion needs (72.1% vs 41.3%; $P < .001$), higher demand for multiple allogeneic blood transfusions (14.8% vs 3.7%; $P < .001$), and higher in-hospital mortality (4.9% vs 1.0%; $P = .019$) compared with those who remained only on aspirin, whereas those with ticagrelor withdrawn greater than 72 hours demonstrated no differences from the aspirin only group.[72]

In the same 2016 analysis of 2244 ACS DAPT patients who underwent urgent or elective CABG described previously for clopidogrel, Hansson and colleagues[71] demonstrated a significantly higher rate of major bleeding complications when ticagrelor was discontinued less than 3 days preoperatively compared with discontinuation at 3 to 5 days preoperatively (unadjusted OR, 5.17; 95% CI, 2.89-9.27; $P < .0001$). The authors also reported that mortality was significantly higher in patients with major bleeding complications (9.9% vs 0.7%; unadjusted OR, 14.78; 95% CI, 7.82-27.93; $P < .0001$). Preoperative thrombotic events were not reported, but postoperative thrombotic events before hospital discharge reportedly occurred in 2.3% of the ticagrelor group compared with 2.8% of the clopidogrel group. An analysis of the thrombotic events stratified by the timing of discontinuation of the P2Y12 inhibitor was not reported.

Most recently, and in accordance with prior trials, in 2019 Kremke and colleagues[82] demonstrated that ticagrelor exposure within 72 hours before cardiac surgery was associated with an increased risk of major bleeding complications, defined as the intraoperative transfusion of more than 1000 mL of RBCs, a postoperative bleeding volume greater than 2000 mL, or the need for reexploration for bleeding or cardiac tamponade.

Prasugrel. Like clopidogrel, prasugrel is a prodrug that requires metabolic conversion to an active metabolite, but it has been demonstrated that the metabolism of prasugrel is less negatively affected by individual "low function" CYP polymorphisms, resulting in more consistent platelet inhibition. The duration of action of prasugrel is known to be longer than that of clopidogrel,[16] but the existing data for the optimal timing of its withdrawal before elective cardiac surgical intervention is much less robust than for clopidogrel or ticagrelor.

The 2009 ACC/AHA guidelines recommended a prasugrel washout time of 7 days before an elective cardiac surgical intervention to minimize bleeding, but this was based on expert consensus opinion (level of evidence C).[75]

Results from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON TIMI 38) CABG cohort published in 2012 may have validated the previous expert consensus recommendation that 5 days of prasugrel washout is insufficient. In that cohort of 346 DAPT patients undergoing isolated CABG, P2Y12 inhibitors (prasugrel or clopidogrel) had been discontinued anywhere from 0 to more than 14 days before surgery, but each group was ultimately analyzed as a whole (results not stratified by time from discontinuation). Of note, only 42.2% of the clopidogrel group and 48.5% of the prasugrel group had washout of their P2Y12 inhibitor for more than 5 days preoperatively and only 29.1% of the prasugrel group for more than 7 days. Analyses demonstrated a higher

overall mean chest tube drainage at 12 hours in the prasugrel group (655 ± 580 mL vs 503 ± 378 mL; P = .050), the incidence of platelet transfusion was significantly higher in the prasugrel group (17.96% vs 9.82%; P = .033), and the mean number of platelet units transfused was also higher (0.78 units vs 0.39 units; P = .047). No significant differences were found in RBC transfusion (2.1 units vs 1.7 units; P = .442). A trend toward a higher incidence of surgical reexploration for bleeding in the prasugrel group was detected (11 of 173 patients) compared with the clopidogrel group (4 of 173 patients), but a surgical source of bleeding was identified in 8 of the 11 prasugrel patients and in 3 of the 4 clopidogrel patients, resulting in very small numbers of patients in whom the ongoing bleeding was likely due to coagulopathy.[70]

It remains the recommendation of the 2017 European Society of Cardiology/European Association for Cardio-Thoracic Surgery that discontinuation of prasugrel at least 7 days before elective cardiac surgical intervention "should be considered."[83]

One notable exception to the understanding that continuation of DAPT up to the time of elective cardiac surgery will result in increased perioperative bleeding, rates of transfusion, and need for postoperative mediastinal reexploration is the data provided by Ouattara and colleagues.[84] In this observational study of 217 consecutive ACS patients presenting for CABG with DAPT (clopidogrel plus aspirin) or SAPT (aspirin alone) maintained up to the time of surgery, the use of aprotinin intraoperatively appears to have mitigated the otherwise expected excessive bleeding and increased rates of transfusion and need for postoperative mediastinal reexploration in the DAPT group compared with the SAPT group. The removal of aprotinin from the market in 2007 renders these results nonapplicable to modern practice, and a subsequent prospective attempt to demonstrate a similar effect with tranexamic acid (TXA) in 150 consecutive patients failed to do so.[85]

DRUGS USED FOR INTRAOPERATIVE BLOOD MANAGEMENT

- **Use of synthetic antifibrinolytic agents, such as epsilon-aminocaproic acid (EACA) or tranexamic acid, reduces blood loss and blood transfusion during cardiac procedures and is indicated for blood conservation (Class I, Level A).**
- **Tranexamic acid reduces bleeding and total transfusion during off-pump CABG surgery (Class IIA, Level B-R).**

LYSINE ANALOGUES VS PLACEBO. A large 2017 randomized trial of 4631 patients aimed to clarify the safety and efficacy profile of tranexamic acid (TXA). Patients were given 100 mg/kg TXA after induction, which was reduced to 50 mg/kg in January 2012 after 1392 patients were enrolled. TXA reduced both the need for RBCs (P < .001) and any blood product (P < .001) compared with placebo. The number needed to treat (NNT) for TXA to reduce transfusion of 1 unit of blood products was 6. TXA also reduced the need for reexploration (1.4% vs 2.8%; RR, 0.49; 95% CI, 0.32-0.75; P = .001). There was no significant benefit for 30-day mortality or thromboembolic events. It should be noted that, although it was not a pre-selected outcome in our PICO question, this study raises questions on the association between TXA and seizures.[86]

Other smaller RCTs, such as those by Taghaddomi and colleagues[87] and Esfandiari and colleagues[88] confirmed the benefits of TXA over placebo in reducing bleeding and total transfusions, and the RCTs by Taghaddomi and colleagues[87] and Wang and colleagues[89] suggest that these benefits might extend to off-pump CABG patients as well, although more than 10% of the randomized patients in the study by Wang and colleagues[89] were converted to CPB, and the authors did not perform separate intention-to-treat and per-protocol analyses.

TXA VS EACA. Several studies have been published since the most recent meta-analysis to investigate the effects of TXA vs EACA. Raghunathan and colleagues[90] published a large RCT in 2011 of 1550 patients taken from data published in the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) trial. There was no difference in any outcome between the 2 agents, except a reduction of FFP use in TXA (RR, 0.83; 98.33% CI, 0.72-0.96). The primary outcome of the study, as in the BART trial, was a composite outcome of bleeding from chest tubes that exceeded 1.5 liters during any 8-hour period or massive transfusion, which was defined as the administration of more than 10 units of RBCs within 24 hours after surgery. To detect an absolute difference of 3% in major bleeding based on the results of the trial, the sample size would have to be doubled. Rarer outcomes would have required up to 10,000 patients to detect a clinically-meaningful difference.

The randomized trial by Alizadeh Ghavidel and colleagues[91] included 3 groups of 100 patients, each receiving either TXA, EACA, or placebo. EACA was superior to placebo and TXA at 6 hours, 12 hours, and 24 hours after surgery for total bleeding, although this benefit did not reduce the need for transfusion of RBC, FFP, or platelets at any time point. EACA was superior to placebo at reducing the need for RBCs both intraoperatively and in the ICU, whereas TXA significantly reduced the need for RBCs only in the ICU. There was an unusual amount of demographic and operative differences between the groups for an RCT in this study. The

consistent lack of significant differences between TXA and placebo is likewise a function of lack of statistical power.

The small RCT of 78 patients by Choudhuri and colleagues[92] compared EACA and TXA, and the only outcome of interest reported was a nonsignificant difference between the rate of reexploration for bleeding among the 3 study groups (TXA, n = 2; EACA, n = 2; control, n = 3; $P > .05$). Owing to the relative low quality of this study, the next best evidence is the retrospective cohort study by Keyl and colleagues,[93] which compared 341 patients in each group. TXA was superior at reducing blood loss (logistic regression OR, 0.57; 95% CI, 0.39-0.83; $P = .003$) and preventing the use of blood products (RBCs, $P = .002$; FFP, $P < .001$; and platelets, $P < .001$). This study also raises further questions on the association between TXA and seizures.

Martin and colleagues[94] also compared TXA vs EACA in a 2011 retrospective cohort study of 604 patients. TXA significantly reduced 24-hour blood loss but did not significantly reduce use of any transfusion products, reexploration, 30-day mortality, or thromboembolic events compared with EACA.

A meta-analysis assessing the randomized and nonrandomized data would increase the power to detect a difference between TXA and EACA, but it does not appear at this time that one agent is meaningfully superior to another.

The lysine analogues TXA and EACA remain viable alternatives for safely reducing total blood loss associated with cardiac surgery, the rate of transfusion, and the total amount of blood products used in transfusion. The effect of these agents on 30-day mortality, reexploration due to bleeding, and thromboembolic events is not clearly established vs control. The association between TXA and seizures is noted and will be a point of emphasis for this guideline in the future.

CONTINUING RESEARCH ON APROTININ VS PLACEBO AND VS LYSINE ANALOGUES. Despite the fact that aprotinin has been off the market in the United States and Europe since the BART study in 2008 due to safety concerns,[95] our search identified 5 meta-analyses, 2 prospective randomized studies, and 2 retrospective observational studies published since the 2011 Blood Conservation Guidelines that continue to assess its safety and effectiveness either vs other antifibrinolytic agents or vs placebo. Since the BART study, some have suggested that the withdrawal of aprotinin has been detrimental to patient care because of increased adverse outcomes from surgery and increased use of blood products, and the drug has been made available to clinicians in Canada and Europe, albeit with warnings and limited indications.[96]

Two meta-analyses were published in 2009, both heavily influenced by the data from the BART study. Henry and colleagues[97] found no difference in rates of exploration, myocardial infarction, or 30-day mortality between aprotinin and either TXA or EACA, while aprotinin was more effective than EACA at preventing transfusion. McIlroy and colleagues[98] similarly found no increase in mortality or thromboembolic events vs placebo.

Complicating matters further, the meta-analyses by Ngaage and Bland[99] and Hutton and colleagues[96] demonstrated a benefit in TXA vs aprotinin in 30-day mortality, which held for RCT-only data and when combined with observational trials. However, the most recent network meta-analysis in 2013 by Howell and colleagues[100] similarly investigated the safety of aprotinin compared with TXA and EACA and found no significant benefit for any agent in 30-day mortality, either compared with each other or placebo.

Two small prospective RCTs and 2 retrospective studies performed after these meta-analyses in 2012 did not clarify the safety profile of aprotinin.[101-104]

The authors of this guideline were not anticipating the extensiveness of the new data on the safety of aprotinin and did not select renal injury in any of the PICO questions. We thus cannot comment on data pertaining to those outcomes. Owing to aprotinin being unavailable to most of the readership for this document, we declined to make a recommendation based on this evidence review.

TOPICAL HEMOSTATIC AGENTS

- **Topical application of antifibrinolytic agents to the surgical site after CPB is reasonable to limit chest tube drainage and transfusion requirements after cardiac operations using CPB. (Class IIA, Level B-R)**

Despite widespread use in cardiac procedures over many years, no single topical preparation emerges as the agent of choice for localized bleeding that is difficult to control. The development of intraoperative bleeding scales[105] may be helpful in determining which hemostatic agent is more likely to be useful in certain situations, but nevertheless, the source of bleeding and the patient's coagulation profile are important factors that may preclude the actions of any and all topical hemostatic agents. Assessment of topical hemostatic agents in clinical RCTs is extremely difficult due to difficulty in establishing reliable end points, and using reproducible bleeding scales intraoperatively may be the best method to compare efficacy of topical hemostatic agents.

INTRAOPERATIVE NONPHARMACOLOGIC INTERVENTIONS

SURGICAL APPROACH. When determining the desired treatment for a patient with an ailing medical condition, several factors play into the treatment strategy

recommended. Survival, symptom relief, and the avoidance of serious adverse events (stroke and myocardial infarction) are given the most weight in the strategy chosen.[106] Although efforts to minimize bleeding are part of the equation, rarely would bleeding risk attributable to a particular procedure be the primary factor with respect to decisions around competing treatment options. A patient's absolute refusal of blood products for faith-based reasons or otherwise would be the key exception to this rule. Still, knowledge with respect to bleeding risk for competing therapies is important, because blood transfusions can be both life-saving and deleterious to a patient depending on the context of the situation.[27] In general, if improved or equivocal outcomes can be attained with a particular treatment relative to an alternative, and the need for transfusions is significantly less, such a therapy is looked upon favorably. For cardiac surgery, the above interplay is most relevant to decision making with respect to thoracic aortic endografts, transcatheter valve technologies, minimal-access surgical techniques, and off-pump coronary surgery.

With respect to thoracic aortic endografts and off-pump coronary surgery, the effectiveness of these interventions to reduce bleeding were acknowledged in the 2011 Blood Conservation Practice Guidelines[59] and are again supported in this updated document, with the caveat that formal recommendations are being withheld in this version. Insertion of aortic endografts for thoracic aortic disease is a major advancement in blood conservation for what is an otherwise complex high-risk patient population. In a very similar manner, transcatheter valve technologies are revolutionizing the treatment of structural heart disease and have also proven to reduce the need for blood transfusions.[107] Further, although minimal-access surgery is a heterogenous conglomerate of variable techniques, which impedes efforts for quality scientific assessment, best evidence would attribute a blood conservation advantage to these minimal-access procedures [108,109]

Off-pump coronary surgery has consistently proven to reduce blood transfusions relative to on-pump coronary surgery.[110,111] Yet, given variable results with respect to graft patency[111] and 5-year survival outcomes with off-pump procedures,[112,113] routine use of this technique should be reserved for surgeons making a concerted commitment to integrate off-pump techniques into their daily operative practice.

POC HEMOSTASIS TESTING

- **Goal directed transfusion algorithms that incorporate point-of-care testing, such as with viscoelastic devices, are recommended to reduce periprocedural bleeding and transfusion in cardiac surgical patients. (Class I, Level B-R)**

Abnormalities of hemostasis that place patients at risk for both bleeding and thrombotic events can be the result of inherited defects or acquired conditions. The most common acquired condition in cardiac surgical patients is the induced derangement of coagulation that occurs due to blood contact with the extracorporeal circuit. This includes dilution and depletion of coagulation factors, platelet activation and dysfunction, and fibrinolysis. Also contributing are disease states and use of anticoagulant or antithrombotic drug therapy. New anticoagulant drugs are often potent, and an antidote may not be available. POC monitoring of the hemostatic mechanism is critical to provide timely and accurate assessment of the cause of bleeding, with potential to provide targeted therapies.

The timing of surgery has been optimized in many studies using POC assessment of residual platelet inhibition due to antithrombotic drugs. Viscoelastic tests are used for this purpose and constitute much of the data that have been published on POC testing of hemostasis in cardiac surgery, POC testing is an essential tool that has been used in clinical practice for decades and provides fast results at the bedside. Viscoelastic tests have been used to measure activated clotting times in certain instruments; however, these measures are not recommended to supplant the traditional activated clotting times measurements.[114] Data supporting the use of viscoelastic testing will be presented without regard to the specific platform or instrument used and will be reported based on the strength of the evidence. POC assessment of hemostasis is used to guide blood product administration and can reduce unnecessary transfusions by using a patient-directed approach to transfusion therapy. Viscoelastic testing has been shown to decrease costs by reducing transfusions[115,116] and the risks associated with transfusions.[117,118]

Routine plasma-based coagulation testing results have a poor correlation and limited value in the perioperative management of patients with coagulopathic bleeding.[119,120] These tests are performed on plasma and only represent the time to initiation of clot formation and do not provide data on the platelet-fibrinogen interaction in clot formation. Furthermore, these tests are often sent to a central laboratory, which increases turnaround time and renders them not ideal for prediction or management of perioperative hemorrhage. Given these limitations, the use of viscoelastic POC coagulation assays to predict excessive bleeding and guide hemostatic therapies in patients with suspected coagulopathy has significantly increased over the last 2 decades and has been incorporated into numerous PBM algorithms.

The use of POC-based transfusion algorithms using viscoelastic testing have resulted in a significant reduction of allogeneic blood product transfusion in high-risk

clinical settings such as cardiovascular surgery.[121] A large prospective multicenter trial by Karkouti and colleagues[122] included more than 7000 cardiac surgery patients. The trial analyzed transfusion rates before and after implementation of a viscoelastic testing-based transfusion algorithm plus a platelet function analyzer. The use of a POC-based transfusion algorithm resulted in a significant decrease in RBC and platelet transfusions. When used in conjunction with a specific POC platelet function analyzer, algorithms have demonstrated a significant blood-sparing effect when compared prospectively with standard laboratory testing.

Many studies that incorporate viscoelastic-based transfusion algorithms and demonstrate reduced transfusions substitute the early use of prohemostatic factor concentrates and fibrinogen concentrate for allogeneic blood.[117] This practice reduces transfusions; however, the use of PCCs and fibrinogen concentrate in place of blood products must be carefully evaluated for safety.[123] This renders careful monitoring of hemostasis a critical part of this practice.[124]

Meta-analyses and systematic reviews evaluating the efficacy of POC viscoelastic testing to guide management indicate that this intervention reduces bleeding and reduces transfusion rates but alone does not have a demonstrable effect on morbidity.[125,126] Whether the individual investigations were powered to evaluate the impact of viscoelastic testing on morbidity and mortality is questionable. These systematic reviews have evaluated the data published using the first viscoelastic tests to be commercially penetrant. It is feasible that similar results can be accomplished with the more modern devices,[127,128] but these large-scale studies have not yet been conducted.

PERFUSION INTERVENTIONS

ACUTE NORMOVOLEMIC HEMODILUTION

- **Acute normovolemic hemodilution is a reasonable method to reduce bleeding and transfusion. (Class IIA, Level of Evidence A)**

CPB is responsible for multiple negative effects on circulating blood and blood components. Acute normovolemic hemodilution (ANH) is a method to limit these effects on a portion of the patient's blood volume. Although there are no published standardized protocols for ANH, it typically involves the removal of 1 to 3 units of the patient's blood before heparinization. Currently, ANH is an underused method in cardiac surgery. An observational study by Goldberg and colleagues[129] showed that ANH was performed in only 17% of patients before surgery. The reason for its underuse may be because it requires additional preoperative time, possible lack of attention to PBM strategies in general, and real or perceived risks of ANH. Additionally, benefits of ANH are directly linked to the amount of whole blood that is withdrawn from the patient.[129-131] Lack of established protocols for removal of blood, hemodynamic support, and indications and contraindications may also be a roadblock to widespread use.

Although ANH has been used for many decades, it is not until recently that RCTs and meta-analyses have been published. In a 2017 meta-analysis, Barile and colleagues[132] combined data from 2439 patients from 29 RCTs. Patients who underwent ANH had an estimated 388 mL total blood loss vs 450 mL in the control groups (mean difference, −0.64; 95% CI, −0.97 to −0.31; $P < .001$) and a 26% reduced risk (absolute risk reduction, 14%) of transfusion (RR, 0.74; 95% CI, 0.62-0.87; $P < .001$).[132] ANH was also associated with 0.79 fewer units of RBCs used. The conclusions of this study are limited by a very high degree of heterogeneity, which was due to differences in the amount of blood removed, the types of surgery, year of publication, and presence/absence of a transfusion protocol among the included studies. The size of the effect suggests to this group that there is likely a benefit to using ANH; however, the extent of that benefit is unclear.

When ANH is used with adequate volumes, there is an apparent decrease in perioperative blood and blood product use. Consistently, the greater the amount of whole blood that can be removed from the patient without hemodynamic instability, the greater the effects of ANH.[129] Care must be taken in patients who are preoperatively anemic, smaller patients who may have lower overall blood volumes, and stable patients who are prone to instability (ie, left main disease) and unstable patients. It is also important to avoid profound anemia while on CPB, although blood that has been removed can be reinfused into the patient at any time, including while on bypass, to prevent deleterious effect of severe anemia.

In efforts to maintain acceptable hematocrit levels during CPB, it may be useful to combine ANH with retrograde autologous priming (RAP). In the retrospective study of more than 18,000 patients by Stammers and colleagues,[130] comparisons were made between patients that had RAP only, ANH only, RAP and ANH, or neither. The lowest transfusion rates were seen in the ANH-only cohort while the highest transfusion rates were seen in the neither patients.[130] As a retrospective study, and as in many studies when it comes to blood conservation, drawing firm conclusions is difficult due to patient acuity differences as well as physician and institutional commitment to a comprehensive multimodality approach to PBM.

Further studies are required to standardize the methods of ANH so that they can be more broadly applied. Nevertheless, it is apparent that ANH is an effective way to limit the deleterious effects of CPB on at least a portion of the patient's blood volume, leading to a decreased need for transfusions in cardiac surgery.

RETROGRADE AUTOLOGOUS PRIMING

- **Retrograde autologous priming of the CPB circuit should be used wherever possible. (Class I, Level B-R)**

Multiple small randomized prospective studies and a moderately sized meta-analysis suggest that RAP is a simple, safe, and effective process to decrease intraoperative and postoperative transfusion rates, especially for preoperative anemia and those procedures that result in excessive blood loss. Although studies consistently report lower transfusion rates in the RAP groups, improvements in mortality and complication rates are not confirmed when RAP is considered as the sole difference in surgical therapy.

A 2009 meta-analysis by Saczkowski and colleagues[133] of 557 patients in 6 trials concluded that patients in the RAP group had both fewer intraoperative transfusions (OR, 0.36; 95% CI, 0.13-0.94; $P = .04$) and fewer transfusions during their total stay (OR, 0.26; 95% CI, 0.13-0.52; $P = .0001$), with an NNT of 11 during the intraoperative period and 4 for the total stay. The study further reported a weighted mean difference of −0.60 units of RBCs used (95% CI, −0.90 to −0.31 units). Each of the 6 individual studies that made up the analysis scored poorly on the rating scale performed by the authors (Appendix 4), and there was some moderate heterogeneity in the intraoperative data. This may result in an overestimate of the effect size for RAP.[133]

In a randomized, prospective study by Hofmann and colleagues,[134] intraoperative rates of transfusions were 17.2% in the non-RAP group vs only 3.7% in the RAP group, with an absolute risk reduction of 13.5 and an NNT of 7.44. No significant differences in the amount of bleeding, mortality, reexploration, or thromboembolic events were found. Likewise, a 2015 RCT by Cheng and colleagues[135] reported reductions in perioperative transfusion rates of 54.2% for RAP and 95.8% for non-RAP ($P < .01$). There were no significant differences in the amount of bleeding in this trial.[135]

Throughout most recent studies, the volume that is removed is an important criterion contributing to the effectiveness of RAP in reducing blood transfusions. Maintenance of hemodynamic stability is achieved by physical (Trendelenburg positioning) and/or pharmacologic (vasoconstrictors) means. No recent studies show any increased risk from intraoperative RAP, and as such, the risk/benefit ratio is significantly in favor of RAP for patients at risk.

MINICIRCUITS

- **Reduced priming volume in the CPB circuit reduces hemodilution and is indicated for blood conservation. (Class I, Level B-NR)**
- **Minimally invasive extracorporeal circulation is reasonable to reduce blood loss and red cell transfusion as part of a combined blood conservation approach. (Class IIA, Level B-R)**

Two recent large registry studies provide insight on the impact of prime volume on hemodilution and transfusion. Sun and colleagues[136] demonstrated in a 2017 registry study with more than 47,000 patients that the ratio of prime volume to estimated blood volume was an independent predictor of transfusion, with increased ratios (larger prime volumes) resulting in transfusion. Similarly Dickinson and colleagues,[137] in a 2019 study evaluating more than 21,000 patients, showed that exposure to larger net prime volumes indexed to body surface area was an independent predictor of an increased risk of transfusion. Each of these studies demonstrated associations of reduced hemodilution with decreased prime volume.

The adoption of a combined strategy of surgical approach, anesthesia, and perfusion management, along with CPB circuit features designed to minimize hemodilution and optimize biocompatibility, has been termed minimally invasive extracorporeal circulation (MiECC). Configuration of the circuit components for MiECC have been defined by consensus to include a combination of multiple techniques, including a closed CPB circuit, biologically inert blood contact surfaces, reduced priming volume, a centrifugal pump, a membrane oxygenator, a heat exchanger, a cardioplegia system, a venous bubble trap/venous air-removing device, and a shed blood management system.[138]

Two meta-analyses, in 2011 and 2013, supplemented by 3 additional RCTs, provide evidence for blood conservation benefits associated with MiECC. The meta-analyses compared MiECC and studies using conventional CPB in both CABG and valve operations in 29 and 24 studies, respectively, with 18 studies in common.[139,140] Both meta-analyses reported reduced RBC transfusion (OR, 0.35; 95% CI, 0.23-0.53; $I^2 = 0$; and OR, 0.24; 95% CI, 0.16-0.37; $I^2 = 5\%$), and failed to show any difference in reoperation for bleeding. Blood loss in both studies was also reduced, albeit with substantial heterogeneity (weighted mean difference [WMD], −131.32; 95% CI, −187.87 to −74.76; $I^2 = 89\%$; and WMD, −137.93; 95% CI, −198.98 to −76.89; $I^2 = 81\%$). Both meta-analyses reported no differences in 30-day mortality, myocardial infarction, renal, and cerebral outcomes.

Three additional RCTs with sample sizes of more than 100 have been reported, which support the findings of the previously published meta-analyses. The 2011 trial by El-Essawi and colleagues[141] of 500 patients demonstrated a decreased RBC transfusion requirement in the MiECC group (199 ± 367 mL vs 347 ± 594 mL, $P < .001$), reoperation for bleeding (2.4% vs 6.1%; $P < .05$), with transfusion as a whole (35.3% vs 44.8%), transfusion of packed RBCs (28.6% vs 39.5%), and transfusion of FFP (17.5% vs 25.4%) all significantly lower in the MiECC patients ($P = .04$, $P = .01$, and $P = .04$, respectively). Anastasiadis and colleagues[142] (2013), in an RCT of 120

patients, reported lower intraoperative blood transfusion (0.5 ± 0.7 units vs 1.5 ± 1.1 units; $P < .001$) and postoperative blood transfusion (2 ± 1.7 units vs 3 ± 2.4 units; $P = .009$) in the MiECC group.[142] Baumbach and colleagues[143] evaluated 200 patients undergoing minimally invasive mitral valve replacement/aortic valve replacement surgical approaches and found total red cell transfusion to be reduced in the MiECC group (1.06 ± 1.95 units vs 1.67 ± 1.80 units; $P = .003$), while reporting no other clinical outcome differences apart from reduced delirium in the MiECC group.

Significant confounders impact much of this literature, the most important of which is the composition of the control groups used to compare MiECC. The control circuits invariably have high prime volumes, nonbiocompatible-coated circuits, and limited access to cell salvage, making the interpretation of these data difficult. Additionally, there is large variability in the reporting of transfusion-related outcomes, often small sample sizes, and unclear methods of randomization, all of which contribute to the variable inclusion of papers in the 2 meta-analyses.

POSTOPERATIVE MANAGEMENT

TRANSFUSION TRIGGERS

- **In patients undergoing cardiac surgery, a restrictive perioperative allogeneic RBC transfusion strategy is recommended in preference to a liberal transfusion strategy for perioperative blood conservation, as it reduces both transfusion rate and units of allogeneic RBCs without increased risk of mortality or morbidity. (Class I, Level A)**
- **Allogeneic RBC transfusion is unlikely to improve oxygen transport when the hemoglobin concentration is greater than 10 g/dL and is not recommended. (Class III: No Benefit; Level B-R)**

Since the publication of the 2011 Guidelines, several RCTs involving more than 8000 patients have investigated the use of restrictive vs liberal RBC transfusion strategies in patients undergoing cardiac surgery.[144-148] These studies have originated from 4 different countries and involved patients from all continents in the world. Although there were some differences in design, such as preoperative vs postoperative randomization and superiority vs noninferiority comparisons, all included a restrictive trigger between 7 and 8 g/dL and a liberal trigger between 8 and 10 g/dL, and all had primary and secondary outcomes that included important clinical events such as morbidity, mortality, and resource utilization, including blood product exposure.

The Transfusion Requirements After Cardiac Surgery (TRACS) study randomized 502 cardiac surgery patients in Brazil to a restrictive (hematocrit 24%) or liberal (hematocrit trigger 30%) RBC transfusion strategy while in the operating room and ICU.[144] Patients in the liberal group received significantly more transfusions than the restrictive group (78% vs 47%), and there was no difference in the primary composite end point of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration). These outcomes also did not significantly differ individually. However, the trial was not powered to detect these differences; thus, these results should be interpreted cautiously. Nevertheless, the P value of 0.93 for the 1% absolute difference in 30-day mortality (6% liberal vs 5% restrictive) suggests that a meaningful clinical difference is very unlikely.

Another study randomized 722 adults in the United States and India who were having valve or CABG surgery to a restrictive (24% hematocrit) or liberal (28% hematocrit) transfusion threshold.[146] The restrictive group received significantly fewer allogeneic transfusions (54% vs 75%; $P < .001$). The study was stopped at the preplanned interim analysis at which time it was deemed futile to be able to achieve a difference in the primary composite outcome of in-hospital postoperative morbidity and mortality.

The Transfusion Requirements in Cardiac Surgery III (TRICS III) trial randomized more than 5000 adults undergoing moderate- to high-risk cardiac surgery with CPB to a restrictive transfusion strategy (hemoglobin transfusion threshold <7.5 g/dL) or a liberal one (threshold <9.5 g/dL in the operating room and ICU; <8.5 g/dL on the ward).[148] RBC transfusion occurred in 52.3% of the restrictive patients compared with 72.6% of the liberal group (OR, 0.41; 95% CI, 0.37-0.47; $P < .001$). Noninferiority of the restrictive group was confirmed for the primary composite outcome of death, myocardial infarction, stroke, or dialysis at the earlier of 28 days or hospital discharge. The results were similar after 6 months of follow-up, with no differences between groups in the components of the primary outcome or an expanded outcome, which included emergency department visits, rehospitalization, or coronary revascularization.[148]

In the Transfusion Indication Threshold Reduction (TITRe2) trial, 2007 patients who had undergone cardiac surgery with a postoperative hemoglobin level of less than 9 g/dL were randomized to a transfusion threshold of 7.5 g/dL (restrictive strategy) or 9 g/dL (liberal strategy).[145] The transfusion rate after randomization was significantly lower in the restrictive group (53% vs 92%). There was no difference in the primary composite outcome of infection and ischemic events within 3 months of surgery, although mortality was 1.6% lower in the liberal group (HR, 1.64; 95% CI, 1.00-2.67; $P = .045$). Although it is a secondary analysis, this safety outcome

in a large, multicenter trial stands in contrast with the rest of the randomized data. Thus, the several meta-analyses performed since the most recent guidelines are better positioned to confirm or refute the equivalence of the two strategies.

As expected in these recent systematic reviews and meta-analyses, restrictive transfusion significantly reduced the number of patients receiving a RBC transfusion.[149-151] The probability of receiving an allogeneic transfusion was significantly reduced by approximately 30% with restrictive transfusion (RR, 0.69; 95% CI, 0.67-0.71), and the transfusion risk was thus approximately 1.5-times higher in the liberal group. The average amount of transfusion was reduced by approximately 1 unit (WMD, 0.87-0.90 units), and there was no significant difference in blood loss.

Although there were slight differences in the data analyses undertaken, all meta-analyses found no difference in mortality between transfusion strategies (ORs or RRs from 0.96 to 1.03) with low heterogeneity (I^2 = 0%-21%). No significant subgroup interactions or heterogeneity were identified for type of surgery (elective vs nonelective), patient category (adult vs pediatric), or time of randomization (preoperative/intraoperative vs postoperative).[150,151] Two of the systematic reviews included trial sequential analyses which demonstrated that the total sample size accumulated from the randomized trials undertaken to date was sufficient to ultimately conclude that restrictive transfusion was not inferior to the liberal strategy (and conversely that liberal was not superior to restrictive) in terms of mortality.[151,152] Furthermore, there were no significant differences between restrictive and liberal transfusion in reoperations, myocardial infarction, and stroke.

Overall, the best evidence from multiple recent randomized controlled trials, systematic reviews, and meta-analyses clearly establishes that the use of restrictive RBC transfusion strategies reduces both the probability and amount of RBC transfusion without increasing the risk of mortality or major morbidity in patients undergoing cardiac surgery.

FLUID MANAGEMENT

- **It is reasonable to administer human albumin after cardiac surgery to provide intravascular volume replacement and minimize the need for transfusion. (Class IIA, Level B-R)**
- **Hydroxyethyl starch is not recommended as a volume expander in cardiopulmonary bypass patients as it may increase the risk of bleeding. (Class III: No Benefit, Level B-R)**

Fluid boluses are common and responsible for a large proportion of the positive fluid balance seen in patients after cardiac surgery.[153] The most common reason for fluid administration was hypotension (65%), and crystalloid fluid was used for 65% of the boluses.[153] Crystalloid solutions that are commonly used in cardiac surgery are 0.9% (normal) saline and buffered isotonic crystalloid solutions. There is evidence that the use of 0.9% saline may be associated with increased blood transfusion requirements compared with buffered crystalloids in nonsurgical patient populations[154-157] as well as with a heightened risk of acidosis with high volumes in animal models.[158] Comparisons between saline and a buffered isotonic crystalloid solution in cardiac surgery patients can be found in post hoc subgroup analyses conducted within a multicenter, double-blind study and a prospective, single-center nested-cohort study. The analyses found no differences between saline and buffered crystalloid in chest drain output, and the buffered crystalloid group actually received more transfusions.[159] These results, however, were not intended to be more than hypotheses-generating for a more direct study.

For colloids, albumin has been used extensively after cardiac surgery. Some evidence exists for increased adverse outcomes in trauma and sepsis patients,[160] although this has not yet been corroborated in cardiac surgical populations. A sequential period open-label pilot study of 100 adult cardiac surgery patients demonstrated that postcardiac surgery fluid bolus therapy with 20% albumin compared with crystalloid fluid resulted in less positive fluid balance as well as several hemodynamic and ICU treatment advantages.[161] Another randomized prospective study of 240 elective cardiac surgery patients showed that despite equal blood loss from chest drains, albumin interfered with blood coagulation and produced greater hemodilution, which was associated with more transfusion of blood products compared with crystalloid use only.[162] Two retrospective studies implementing albumin reduction strategies found no difference in mortality and transfusion between crystalloid and albumin groups.[163,164] Interestingly, a retrospective cohort study of 984 patients undergoing on-pump cardiac surgery showed a dose-dependent acute kidney injury risk associated with the administration of albumin.[165] These retrospective studies carry significant limitations due to lack of vigorous variable control.

The extensive restriction of another commonly used colloid solution in cardiac surgery, hydroxyethyl starch (HES), was recommended by the European Medicines Agency in 2013 and mandated a change in volume management in cardiac surgery.[166] A meta-analysis was performed of postoperative blood loss in randomized clinical trials of HES vs albumin for fluid management in adult CPB surgery. Included in the meta-analysis were 18 randomized trials with 970 total patients reported from 1982 to 2008, and the median number of patients per

trial was 48 (interquartile range, 30-60 patients). The indications for colloid use were volume expansion in 9 of the trials, pump priming in 5, and both in 4. HES increased blood loss, reoperation for bleeding, and blood product transfusion after CPB. There was no evidence that these risks could be mitigated by lower molecular weight and substitution.[167]

In contrast, another meta-analysis of RCTs could not identify safety issues with tetrastarches compared with albumin or crystalloid solutions in blood loss, transfusion requirements, or hospital length of stay in patients undergoing cardiac surgery.[168] This meta-analysis included 51 publications describing 49 clinical studies composed of an aggregate of 3439 patients until July 2013. Of these 49 studies, 30 were unblinded, 10 were partly blinded, and 9 were completely blinded. The duration of follow-up covered a wide range, from 2 hours to 30 days. The variations in inclusion of studies might explain the apparent differences in conclusions.

In a randomized, double-blind controlled trial of 262 patients, use of HES for volume resuscitation after cardiac surgery improved hemodynamic status, but the HES group received more plasma transfusions.[169] A small prospective randomized trial of 45 patients demonstrated that even a small dose of HES 130/0.4 impaired clot strength after cardiac surgery in a dose-dependent fashion but did not increase blood loss.[170] A prospective observational study of 90 patients found that HES 130/0.4 did not affect blood coagulation in cardiac surgery.[171] In a randomized prospective blinded trial, HES was found to interfere with blood coagulation and produced greater hemodilution, which was associated with more transfusion of blood products compared with crystalloid use only.[162]

Two RCTs in the intensive care setting—the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) and Scandinavian Starch for Severe Sepsis/Septic Shock Trial (6S) trial[172,173]—found that tetrastarches increased the use of dialysis and blood transfusion products; furthermore, the 6S trial, which focused on patients with severe sepsis, found an 8% higher 90-day mortality associated with tetrastarches. Routine cardiac surgery patients, however, were excluded from these trials.

In a multicenter prospective cohort study, intraoperative and postoperative use of HES 130/0.4 was not associated with increased risks of acute kidney injury and dialysis after cardiac surgery.[174] Two small trials further confirmed the lack of renal injury from HES.[175,176] A retrospective cohort study found a lower dose of HES was significantly associated with a reduced incidence of acute renal injury and recommended that the cumulative dose of modern HES in cardiac surgery should be kept less than 30 mL/kg.[177]

MASSIVE TRANSFUSION. A recent study provided some helpful prediction algorithms and management options for patients at higher risk of massive transfusion.[178] Risk factors for massive transfusion common to valve surgery alone, CABG alone, and their combination were identified. They include female sex, older age, renal dysfunction, lower body mass index, lower preoperative hemoglobin, and longer CPB times. Several independent massive transfusion risks were identified specific to valve surgery and include active endocarditis, nonatrial fibrillation, smaller left atrium diameter, abnormal international normalized ratio, and repeat operations. Different types of cardiac operations share several, but not all, massive transfusion risk factors.

The ratio of FFP to RBC is a topic of discussion both in cardiac surgery and in major trauma. In trauma, there is a well-recognized benefit from 1:1 ratio of FFP to RBC in patients with major hemorrhage related to trauma. This ratio is less well established in patients undergoing cardiac operations. One observational study evaluated the ideal ratio of FFP to RBC in patients undergoing major cardiac operations requiring massive transfusion.[179] These authors found that higher FFP/RBC ratios (sometimes approaching >1:1 ratio) were associated with reduced risk of death, stroke, and myocardial infarction only in patients undergoing cardiovascular operations and receiving massive transfusions (defined as >10 units of packed RBCs in 1 postoperative hour). This less-than-rigorous evidence provides modest support for adherence to a 1:1 ratio of FFP/RBC in massively bleeding cardiac surgery patients after operations as an extension from the trauma literature. This recommendation must be tempered with caution, because even trauma surgeons have concerns about optimal transfusion therapy and evaluation of traumatic hemorrhage.[180]

BLOOD SALVAGE. Intraoperative blood salvage using cell-saving technology is a well-established method of recovering shed blood during cardiac procedures. The techniques used to harvest intraoperative shed blood have some risks, including bacterial contamination, but consensus suggests that benefits outweigh risks, especially in operations with anticipated large blood loss, including cardiac procedures. Autologous blood salvage in cardiac operations is a tool for perioperative blood conservation.[181] Clinical studies are discordant regarding the benefit of RBC salvage use during and after cardiac operations.[182,183] However, meta-analysis and several observational studies suggest reduced need for homologous blood transfusion associated with intraoperative blood salvage, but no effects on mortality and morbidity.[183,184]

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