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Original Articles

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

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Owing to the constantly evolving nature of the medical literature, the Society of Thoracic Surgeons (STS) clinical practice guidelines periodically undergoes evaluation and updating. A multidisciplinary panel of experts was convened by the 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 STS and the SCA 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. In addition, 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 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 course. Although clinical practices have evolved through the centuries since Dr. William Harvey discovered the circulation of blood in 1,628 and attempted the first blood transfusion thereafter,

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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 most blood products transfused.	Class I, Level A
It is reasonable to discontinue low-intensity antiplatelet drugs (e.g., aspirin) only in purely elective patients without ACS before operation with the expectation that blood transfusion will be reduced.	Class IIA, Level A
Minimization of phlebotomy through 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 CABG patients before 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 (e.g., 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 RBC 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 healthcare 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

there is significant variability in the practices of blood transfusion and conservation in all phases of surgical care. In our current healthcare environment of value-based care, the need for practice guidelines must therefore be further emphasized. In addition, 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, 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 four major tenets of PBM are 1) managing anemia, 2) optimizing coagulation, 3) interdisciplinary blood conservation modalities, and 4) patient-centered decision-making 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. In addition, resource utilization and efficient care have 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 healthcare delivery.

This study 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 different groups and experts. Ultimately, we sought to provide a comprehensive set of

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 most 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 to reduce transfusion burden.	Class IIA, Level B–R
In patients who have 1) preoperative anemia, 2) refuse blood transfusion, 3) or are deemed high risk for postoperative anemia, it is reasonable to administer preoperative ESAs and iron supplementation several days before 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	
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 (e.g., aspirin) only in purely elective patients without ACS before operation with the expectation that blood transfusion will be reduced.	Class IIA, Level A
Laboratory and/or POC measurement of antiplatelet drug effect in patients having received recent DAPT 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 CABG patients before 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 (i.e., administer idarucizumab for dabigatran at appropriate dose or administer andexanet-α for either apixaban or rivaroxaban at an 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 EACA or TXA reduces blood loss and blood transfusion during cardiac procedures and is indicated for blood conservation.	Class I, Level A
TXA reduces bleeding and total transfusion during off-pump CABG surgery.	Class IIA, Level B–R
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
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 (e.g., 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 CPB.	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 FFP 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
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
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 RBC transfusion.	Class IIA, Level A

Table 2. Continued.

Intervention	ACC/AHA Class and Level
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 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 POC 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 healthcare 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

guidelines that are practical and will be received as being reasonable and well researched. Although 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 as 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 1,227 potentially relevant abstracts, which were screened by a group of authors (SF, KK, RSM, and DC). A total of 87 articles met the inclusion criteria. The primary reasons for exclusion were if the population was not relevant (e.g., 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 (SF and KK) developed an evidence table of the relevant articles (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 because of 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 three 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. In addition, 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 the 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 stems from a variety of causes. Routine iron studies are of importance in the determination of the type of anemia present and should be performed 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], .95; p = .01), whereas 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. In addition, 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 three 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, longer intensive care unit (ICU) and hospital lengths of stay (1), and an increase in acute kidney injury (7). However, one retrospective study found only normocytic or macrocytic anemia was associated with increased adverse events (8).

Preoperative Treatment of Anemia—Pharmacologic Agents

- In patients who 1) have preoperative anemia, 2) refuse blood transfusion, 3) or are deemed high risk for postoperative anemia, it is reasonable to administer preoperative erythropoietin-stimulating agents (ESAs) and iron supplementation several days before cardiac operations to increase red cell mass (Class IIA, Level B–R).

Among the difficulties in treatment of the anemic patient oftentimes is the 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 et al. (11) using a regimen of 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 et al. (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, .16; 95% CI, .28–.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 1–2 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). In addition, 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). In addition, 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 ESAs (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], .436; $p < .0005$) and higher hemoglobin on day 4 after surgery (10.2% vs 8.7%; $p < .0005$), although no significant differences were observed 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, .425; $p = .007$), without a significant difference in adverse events, although this study required four 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 B12, 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.

Preoperative Diagnosis and Treatment of Anemia—Nonpharmacologic Interventions

- In patients undergoing cardiac operations, it is reasonable to implement standardized transfusion protocols 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.

The use of preoperative autologous blood donation (PABD) is a theoretically rational approach for patients undergoing elective cardiac procedures using CPB. Although 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 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.

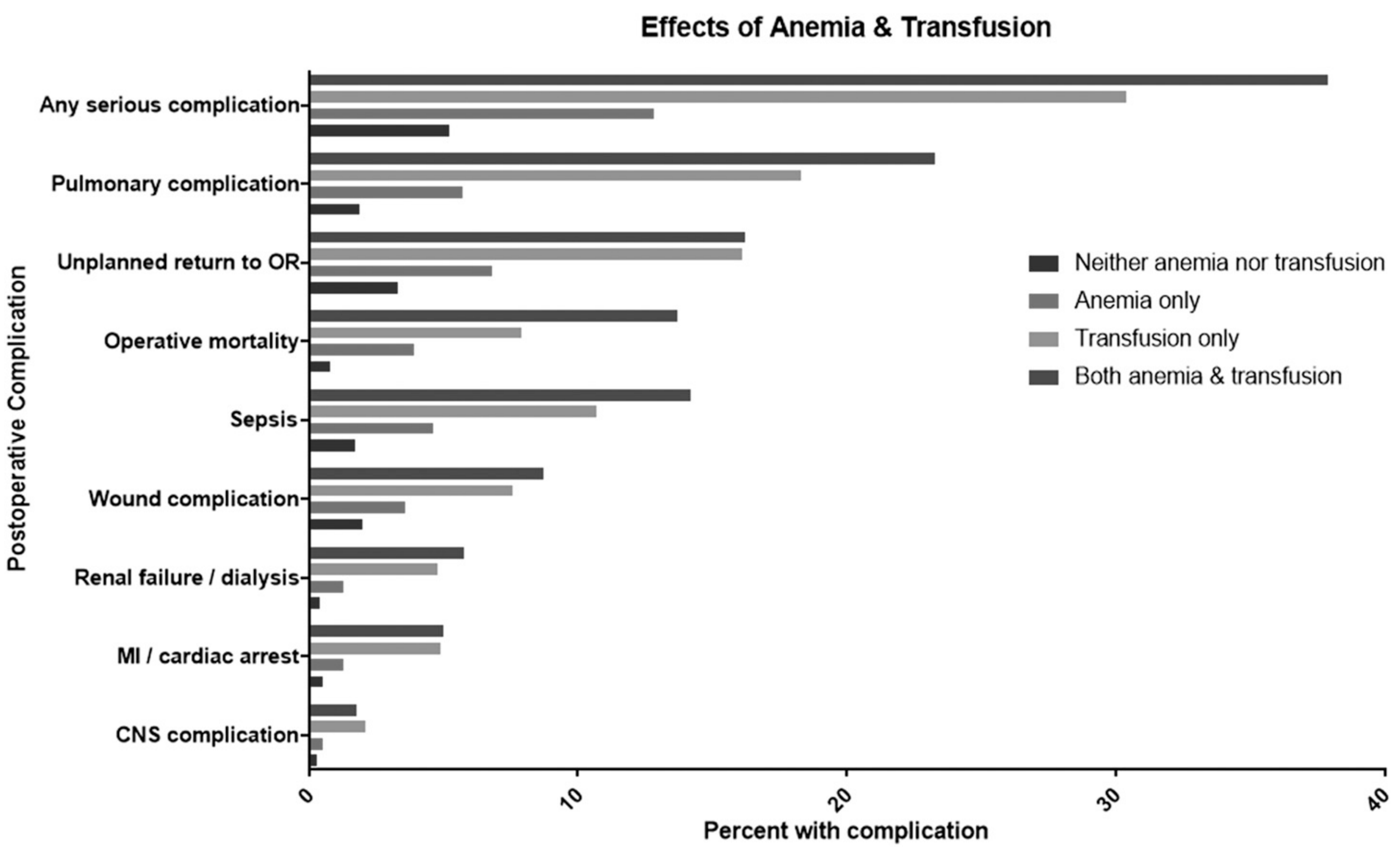

Figure 1. Increased association of adverse outcomes in patients with anemia and/or transfusion. (Reproduced from Ferraris et al. (27) with permission from Elsevier). CNS, central nervous system; MI, myocardial infarction; OR, operating room.

There are 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 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 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 given 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 healthcare 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

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 and EPO
Red cells	Albumin
White cells	Clotting factors
Platelets	Colony-stimulating factors
FFP	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

EPO, erythropoietin; GCSF, granulocyte colony-stimulating factor.

agreed upon, and it should be kept in mind that 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 (i.e., 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 a variable (Class IIA, Level C–LD).
- Prothrombin concentrate is reasonable to consider over FFP 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 two recent retrospective studies confirm increased bleeding complications in the face of preoperative NOAC therapy, with one 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 U.S. Food and Drug Administration has recently approved antidotes for the more widely used NOACs. For dabigatran and 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). Also, 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 PCCs to reduce bleeding in cardiac surgery has been further evaluated since the 2011 guidelines. Already the preferred therapy for emergent warfarin reversal (59), PCCs, may also be applicable in cases of refractory bleeding (60). PCCs 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 two analyses: a propensity score-adjusted multivariate analysis of 971 patients and propensity score-matched cohorts of 225 pairs using PCCs 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 PCCs 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, .41; 95% CI, .16–1.02; $p = .06$). Hospital mortality and reexploration were likewise not statistically significant (62).

A moderate level of evidence suggests that PCCs are 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

- 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 POC measurement of antiplatelet drug effect in patients having received recent dual-antiplatelet therapy (DAPT) can be useful to assess bleeding risk or to guide timing of surgery (Class IIA, Level B–R).

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 (e.g., 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. Furthermore, 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 PCI 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 et al. (80) of five 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 2,632 patients from a larger cohort of 6,385 for other analyses in the five 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%; $p = .01$) than those with less than 5 days of washout. No statistical significance was demonstrated in the all-cause mortality rates between the two treatment groups (3.1% vs. 4.0%; $p = .61$).

More recently, in a 2016 retrospective analysis of prospectively collected data of 2,244 ACS DAPT patients who underwent urgent or elective CABG, Hansson et al. (71) demonstrated that discontinuation of clopidogrel 3–5 days before surgery resulted in a higher rate of major bleeding complications than discontinuation at greater than 5 days preoperatively (unadjusted OR, 1.71; 95% CI, 1.04–2.79; $p = .033$).

Similarly, Tomsic et al. (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 1,000 mL in the first 12 hours postoperatively (26.4% vs. 12.6%; $p < .001$) than 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 exhibits a faster onset and offset of effect, and more consistent inhibition of platelet function than clopidogrel 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 analysis results from the Platelet Inhibition and Patient Outcomes (PLATO) trial suggested that discontinuation of ticagrelor 2–3 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 et al. (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%; $p = .019$) than the subgroup of those who remained only on aspirin, whereas the subgroup of those with ticagrelor withdrawn greater than 72 hours demonstrated no differences from the aspirin-only group (72).

In the same 2016 analysis of 2,244 ACS DAPT patients who underwent urgent or elective CABG described previously for clopidogrel, Hansson et al. (71) demonstrated a significantly higher rate of major bleeding complications when ticagrelor was discontinued less than 3 days preoperatively than discontinuation at 3–5 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. .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 et al. (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 1,000 mL of RBCs, a postoperative bleeding volume greater than 2,000 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 are 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 had washout of their P2Y12 inhibitor 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 (.78 vs. .39 units;

$p = .047$). No significant differences were found in RBC transfusion (2.1 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) than in the clopidogrel group (4 of 173 patients), but a surgical source of bleeding was identified in eight of the 11 prasugrel patients and in three of the four 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 et al. (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, 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 TXA, reduces blood loss and blood transfusion during cardiac procedures and is indicated for blood conservation (Class I, Level A).
- TXA 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 4,631 patients aimed to clarify the safety and efficacy profile of TXA. Patients were given 100 mg/kg TXA after induction, which was reduced to 50 mg/kg in January 2012 after 1,392 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, .49; 95% CI, .32–.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 preselected 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 et al. (87) and Esfandiari et al. (88) confirmed the benefits of TXA over placebo in reducing bleeding and total transfusions, and the RCTs by Taghaddomi et al. (87) and Wang et al. (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 et al. (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 et al. (90) published a large RCT in 2011 of 1,550 patients taken from data published in the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART). There was no difference in any outcome between the two agents, except a reduction in FFP use in TXA (RR, .83; 98.33% CI, .72–.96). The primary outcome of the study, as in the BART, was a composite outcome of bleeding from chest tubes that exceeded 1.5 L 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 et al. (91) included three groups of 100 patients, with each receiving TXA, EACA, or placebo. EACA was superior to placebo and TXA at 6, 12, 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 et al. (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 three 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 et al.

(93), which compared 341 patients in each group. TXA was superior at reducing blood loss (logistic regression OR, .57; 95% CI, .39–.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 et al. (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 because of safety concerns (95), our search identified five meta-analyses, two prospective randomized studies, and two 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 et al. (97) found no difference in rates of exploration, myocardial infarction, or 30-day mortality between aprotinin and either TXA or EACA, whereas aprotinin was more effective than EACA at preventing transfusion. McIlroy et al. (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 et al. (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 et al. (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 two 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 because of 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 aforementioned 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). Furthermore, 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 POC 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 has resulted in a significant reduction in allogeneic blood product transfusion in high-risk clinical settings such as cardiovascular surgery (121). A large prospective multicenter trial by Karkouti et al. (122) included more than 7,000 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 testing–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

ANH

- ANH 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. 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 1–3 units of the patient's blood before heparinization. Currently, ANH is an underused method in cardiac surgery. An observational study by Goldberg et al. (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. In addition, 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 et al. (132) combined data from 2,439 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, −.64; 95% CI, −.97 to −.31; $p < .001$) and a 26% reduced risk (absolute risk reduction, 14%) of transfusion (RR, .74; 95% CI, .62–.87; $p < .001$) (132). ANH was also associated with .79 fewer units of RBCs used. The conclusions of this study are limited by a very high degree of heterogeneity, which was because of 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, stable patients who are prone to instability (i.e., 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 et al. (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, whereas the highest transfusion rates were seen in neither patients (130). As a retrospective study, and as in many studies when it comes to blood conservation, drawing firm conclusions is difficult because of 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 et al. (133) of 557 patients in six trials concluded that patients in the RAP group had both fewer intraoperative transfusions (OR, .36; 95% CI, .13–.94; $p = .04$) and fewer transfusions during their total stay (OR, .26; 95% CI, .13–.52; $p = .0001$), with an NNT of 11 during the intraoperative period and four for the total stay. The study further reported a weighted mean difference of −.60 units of RBCs used (95% CI, −.90 to −.31 units). Each of the six 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 et al. (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 et al. (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 et al. (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 et al. (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 has 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 three 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, .35; 95% CI, .23–.53; $I^2 = 0$; and OR, .24; 95% CI, .16–.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 et al. (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 et al. (142), in an RCT of 120 patients, reported lower intraoperative blood transfusion (.5 ± .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 et al. (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. In addition, 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 articles in the two 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 8,000 patients have investigated the use of restrictive vs. liberal RBC transfusion strategies in patients undergoing cardiac surgery (144–148). These studies have originated from four 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 those in 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 .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 5,000 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, .41; 95% CI, .37–.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 an RBC transfusion (149–151). The probability of receiving an allogeneic transfusion was significantly reduced by approximately 30% with restrictive transfusion (RR, .69; 95% CI, .67–.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, .87–.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 .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 CPB 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 .9% (normal) saline and buffered isotonic crystalloid solutions. There is evidence that the use of .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 post-cardiac 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 than 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. Eighteen randomized trials with 970 total patients reported from 1982 to 2008 were included in the meta-analysis, and the median number of patients per trial was 48 (interquartile range, 30–60 patients). The indications for colloid use were volume expansion in nine of the trials, pump priming in five, and both in four. 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).

By 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 3,439 patients until July 2013. Of these 49 studies, 30 were unblinded, 10 were partly blinded, and nine 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 than 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 gender, 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 one 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).

REFERENCES

1. Klein AA, Collier TJ, Brar MS, et al. The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK – the first association of cardiothoracic anaesthetists national audit. Anaesthesia. 2016;71:627–35.

2. Munoz M, Laso-Morales MJ, Gomez-Ramirez S, et al. Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia. 2017;72: 826–34.
3. von Heymann C, Kaufner L, Sander M, et al. Does the severity of preoperative anemia or blood transfusion have a stronger impact on long-term survival after cardiac surgery? J Thorac Cardiovasc Surg 2016;152:1412–20.
4. Hung M, Besser M, Sharples LD, et al. The prevalence and association with transfusion, intensive care unit stay and mortality of pre-operative anaemia in a cohort of cardiac surgery patients. Anaesthesia. 2011;66:812–8.
5. Spiegelstein D, Holmes SD, Pritchard G, et al. Preoperative hematocrit as a predictor of perioperative morbidities following nonemergent coronary artery bypass surgery. J Card Surg. 2015;30:20–6.
6. Engoren M, Schwann TA, Habib RH, et al. The independent effects of anemia and transfusion on mortality after coronary artery bypass. Ann Thorac Surg. 2014;97:514–20.
7. Oprea AD, Del Rio JM, Cooter M, et al. Pre- and postoperative anemia, acute kidney injury, and mortality after coronary artery bypass grafting surgery: A retrospective observational study. Can J Anaesth. 2018;65:46–59.
8. Dai L, Mick SL, McCrae KR, et al. Preoperative anemia in cardiac operation: Does hemoglobin tell the whole story? Ann Thorac Surg 2018;105:100–7.
9. Peters F, Eveslage M, Gallitz I, et al. Post-operative iron carboxymaltose may have an effect on haemoglobin levels in cardiothoracic surgical patients on the ICU - an observational pilot study about anaemia treatment with intravenous iron. Transfus Med Hemother. 2018;45:42–6.
10. Padmanabhan H, Siau K, Nevill AM, et al. Intravenous iron does not effectively correct preoperative anaemia in cardiac surgery: A pilot randomized controlled trial. Interact Cardiovasc Thorac Surg. 2019; 28:447–54.
11. Yoo YC, Shim JK, Kim JC, et al. Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. Anesthesiology. 2011;115:929–37.
12. Cladellas M, Farre N, Comin-Colet J, et al. Effects of preoperative intravenous erythropoietin plus iron on outcome in anemic patients after cardiac valve replacement. Am J Cardiol. 2012;110:1021–6.
13. Kei T, Mistry N, Curley G, et al. Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: A systematic review and meta-analysis. Can J Anaesth. 2019;66:716–31.
14 Cho BC, Serini J, Zorrilla-Vaca A, et al. Impact of preoperative erythropoietin on allogeneic blood transfusions in surgical patients: Results from a systematic review and meta-analysis. Anesth Analg. 2019;128:981–92.
15 Song YR, Lee T, You SJ, et al. Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: A pilot study. Am J Nephrol. 2009;30:253–60.
16 Tasanarong A, Duangchana S, Sumransurp S, et al. Prophylaxis with erythropoietin versus placebo reduces acute kidney injury and neutrophil gelatinase-associated lipocalin in patients undergoing cardiac surgery: A randomized, double-blind controlled trial. BMC Nephrol. 2013;14:136.
17 Oh SW, Chin HJ, Chae DW, et al. Erythropoietin improves long-term outcomes in patients with acute kidney injury after coronary artery bypass grafting. J Korean Med Sci. 2012;27:506–11.
18 Fisher JW. Pharmacologic modulation of erythropoietin production. Annu Rev Pharmacol Toxicol. 1988;28:101–22.
19 Beattie WS, Wijeysundera DN, Karkouti K, et al. Acute surgical anemia influences the cardioprotective effects of beta-blockade: A single-center, propensity-matched cohort study. Anesthesiology. 2010;112:25–33.
20 Means RT Jr. Clinical application of recombinant erythropoietin in the anemia of chronic disease. Hematol Oncol Clin North Am. 1994; 8:933–44.
21 Weltert L, Rondinelli B, Bello R, et al. A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: Results of a prospective single-blind randomized controlled trial. Transfusion. 2015;55:1644–54.
22 Weltert L, D'Alessandro S, Nardella S, et al Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: A randomized blind controlled study. J Thorac Cardiovasc Surg. 2010;139:621–6; [discussion: 626-627].
23 Penny-Dimri JC, Cochrane AD, Perry LA, et al. Characterising the role of perioperative erythropoietin for preventing acute kidney injury after cardiac surgery: Systematic review and meta-analysis. Heart Lung Circ. 2016;25:1067–76.
24 Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: A prospective randomised trial. Lancet. 2019;393:2201–12.
25 Tezcan B, Bolukbasi D, Saylan A, et al. Effect of dilutional anemia that can be treated with only one unit of red blood cell transfusion on tissue oxygenation in cardiac surgery patients. Turk J Med Sci. 2019;49:1102–8.
26 Ferraris V, Saha SP, Vyas KS, et al. Blood conservation – balancing risks and benefits. In: Frank SM, Waters JH, eds. Patient Blood Management: Multidisciplinary Approaches to Optimizing Care. Bethesda, MD: aABB Press; 2016:345–70.
27. Ferraris VA, Hochstetler M, Martin JT, et al. Blood transfusion and adverse surgical outcomes: The good and the bad. Surgery. 2015;158: 608–17.
28. Padmanabhan H, Siau K, Curtis J, et al. Preoperative anemia and outcomes in cardiovascular surgery: Systematic review and meta-analysis. Ann Thorac Surg. 2019;108:1840–8.
29. Vlot EA, Verwijmeren L, van de Garde EMW, et al. Intra-operative red blood cell transfusion and mortality after cardiac surgery. BMC Anesthesiol. 2019;19:65.
30 Jabagi H, Boodhwani M, Tran DT, et al. The effect of preoperative anemia on patients undergoing cardiac surgery: A propensity-matched analysis. Semin Thorac Cardiovasc Surg. 2019;31:157–63.
31. Yanagawa B, Rocha RV, Mazine A, et al. Hemoglobin optimization for coronary bypass: A 10-year Canadian multicenter experience. Ann Thorac Surg. 2019;107:711–7.
32. Ayoub K, Marji M, Ogunbayo G, et al. Impact of chronic thrombocytopenia on in-hospital outcomes after percutaneous coronary intervention. JACC Cardiovasc Interv. 2018;11:1862–8.
33. Sapiano MRP, Jones JM, Savinkina AA, et al. Supplemental findings of the 2017 national blood collection and utilization survey. Transfusion. 2020;60(Suppl 2):S17–S37.
34. Vassallo R, Goldman M, Germain M, et al. Preoperative autologous blood donation: Waning indications in an era of improved blood safety. Transfus Med Rev. 2015;29:268–75.
35. Martin K, Keller E, Gertler R, et al. Efficiency and safety of preoperative autologous blood donation in cardiac surgery: A matched-pair analysis in 432 patients. Eur J Cardio Thorac Surg. 2010;37: 1396–401.
36. Lim MH, Je HG, Ju MH, et al. Effects of preoperative autologous blood donation in patients undergoing minimally invasive cardiac surgery. Korean J Thorac Cardiovasc Surg. 2019;52:385–91.
37. Zimmermann E, Zhu R, Ogami T, et al. Intraoperative autologous blood donation leads to fewer transfusions in cardiac surgery. Ann Thorac Surg. 2019;108:1738–44.
38. Schloendorff V. Society of New York Hospital. New York, NY: Court of Appeals; 1914:92.
39. Cobbs v. Grant. 505: Supreme Court of California. 1972: 229.
40. Perlin TM. Clinical Medical Ethics: Cases in Practice. Boston, MA: Little Brown & Co.; 1992.
41. The American College of Surgeons (ACS) Committee on Ethics. Statement on Recommendations for Surgeons Caring for Patients Who Are Jehovah's Witnesses. Chicago, IL: American College of Surgeons; 2018.
42. Bodnaruk ZM, Wong CJ, Thomas MJ. Meeting the clinical challenge of care for Jehovah's Witnesses. Transfus Med Rev. 2004;18:105–16.
43. Rogers DM, Crookston KP. The approach to the patient who refuses blood transfusion. Transfusion. 2006;46:1471–7.
44. Stowell CP, Sazama K. Informed Consent in Blood Transfusion and Cellular Therapies: Patients, Donors, and Research Subjects. Bethesda, MD: aABB Press; 2007.

45 Barnes GD, Lucas E, Alexander GC, et al. National trends in ambulatory oral anticoagulant use. Am J Med. 2015;128:1300–5.e2.
46 Zhu J, Alexander GC, Nazarian S, et al. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. Pharmacotherapy. 2018;38:907–20.
47 Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361: 1139–51.
48. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
49. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365: 981–92.
50. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369: 2093–104.
51. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: A practical guide for clinicians. J Thromb Haemost. 2018;16:209–19.
52. Raval AN, Cigarroa JE, Chung MK, et al. Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: A scientific statement from the American heart association. Circulation. 2017;135:e604–33.
53. Gosselin RC, Adcock DM, Bates SM, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost. 2018;118:437–50.
54. Erdoes G, Martinez Lopez De Arroyabe B, Bolliger D, et al. International consensus statement on the peri-operative management of direct oral anticoagulants in cardiac surgery. Anaesthesia. 2018;73: 1535–45.
55. De Caterina R, Ageno W, Agnelli G, et al. The non-vitamin K antagonist oral anticoagulants in heart disease: Section V-special situations. Thromb Haemost. 2019;119:14–38.
56. Hassan K, Bayer N, Schlingloff F, et al. Bleeding complications after use of novel oral anticoagulants in patients undergoing cardiac surgery. Ann Thorac Surg. 2018;105:702–8.
57. Yu PJ, Lin D, Catalano M, et al. Impact of novel oral anticoagulants vs warfarin on effusions after coronary artery bypass grafting. J Card Surg. 2019;34:419–23.
58. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the anticoagulation forum. Am J Hematol. 2019;94:697–709.
59. Ferraris VA, Brown JR, Despotis GJ, et al. 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg. 2011;91:944–82.
60. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: A randomized, plasma-controlled, phase IIIb study. Circulation. 2013;128:1234–43.
61. Cappabianca G, Mariscalco G, Biancari F, et al. Safety and efficacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery. Crit Care. 2016;20:5.
62. Roman M, Biancari F, Ahmed AB, et al. Prothrombin complex concentrate in cardiac surgery: A systematic review and meta-analysis. Ann Thorac Surg. 2019;107:1275–83.
63. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007;28:1598–660.
64 Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/ non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American heart association Task Force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable Angina/non-ST-elevation myocardial infarction) developed in collaboration with the American College of emergency physicians, the society for cardiovascular Angiography and interventions, and the society of thoracic surgeons endorsed by the American association of cardiovascular and pulmonary Rehabilitation and the society for academic emergency medicine. J Am Coll Cardiol. 2007;50: e1–e157.
65. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. Lancet. 2001;358:527–33.
66. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494–502.
67. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. J Am Med Assoc. 2002; 288:2411–20.
68. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: The clopidogrel in unstable angina to prevent recurrent ischemic events (CURE) trial. Circulation. 2004;110:1202–8.
69. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: Results from the PLATO (platelet inhibition and patient outcomes) trial. J Am Coll Cardiol. 2011;57:672–84.
70. Smith PK, Goodnough LT, Levy JH, et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: Risk-adjusted retrospective data analysis. J Am Coll Cardiol. 2012;60:388–96.
71. Hansson EC, Jideus L, Aberg B, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: A nationwide study. Eur Heart J. 2016;37: 189–97.
72. Tomsic A, Schotborgh MA, Manshanden JS, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with dual antiplatelet treatment. Eur J Cardio Thorac Surg. 2016;50: 849–56.
73. Pickard AS, Becker RC, Schumock GT, et al. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. Pharmacotherapy. 2008;28:376–92.
74. Purkayastha S, Athanasiou T, Malinovski V, et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart. 2006;92:531–2.
75. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54: 2205–41.
76. Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on myocardial revascularization of the European society of Cardiology (ESC) and the European association for Cardio-thoracic surgery (EACTS). Developed with the special contribution of the European association of percutaneous cardiovascular interventions (EAPCI). Eur J Cardio Thorac Surg. 2014;46:517–92.
77. Mishra PK, Thekkudan J, Sahajanandan R, et al. The role of point-of-care assessment of platelet function in predicting postoperative bleeding and transfusion requirements after coronary artery bypass grafting. Ann Card Anaesth. 2015;18:45–51.
78. Rahe-Meyer N, Winterhalter M, Boden A, et al. Platelet concentrates transfusion in cardiac surgery and platelet function assessment by multiple electrode aggregometry. Acta Anaesthesiol Scand. 2009; 53:168–75.
79. Wallentin L. P2Y(12) inhibitors: Differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J. 2009;30:1964–77.
80. Cao C, Indraratna P, Ang SC, et al. Should clopidogrel be discontinued before coronary artery bypass grafting for patients with acute coronary syndrome? A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2014;148:3092–8.

81. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: The ONSET/OFFSET study. Circulation. 2009;120:2577–85.
82. Kremke M, Gissel MS, Jensen MJ, et al. The association between a three-day ticagrelor discontinuation and perioperative bleeding complications. Eur J Cardio Thorac Surg. 2019;55:714–20.
83. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardio Thorac Surg. 2018;53: 34–78.
84. Ouattara A, Bouzguenda H, Le Manach Y, et al. Impact of aspirin with or without clopidogrel on postoperative bleeding and blood transfusion in coronary surgical patients treated prophylactically with a low-dose of aprotinin. Eur Heart J. 2007;28:1025–32.
85. Amour J, Garnier M, Szymezak J, et al. Prospective observational study of the effect of dual antiplatelet therapy with tranexamic acid treatment on platelet function and bleeding after cardiac surgery. Br J Anaesth. 2016;117:749–57.
86. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med. 2017;376:136–48.
87. Taghaddomi RJ, Mirzaee A, Attar AS, et al. Tranexamic acid reduces blood loss in off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2009;23:312–5.
88. Esfandiari BR, Bistgani MM, Kabiri M. Low dose tranexamic acid effect on post-coronary artery bypass grafting bleeding. Asian Cardiovasc Thorac Ann. 2013;21:669–74.
89. Wang G, Xie G, Jiang T, et al. Tranexamic acid reduces blood loss after off-pump coronary surgery: A prospective, randomized, double-blind, placebo-controlled study. Anesth Analg. 2012;115: 239–43.
90. Raghunathan K, Connelly NR, Kanter GJ. Epsilon-Aminocaproic acid and clinical value in cardiac anesthesia. J Cardiothorac Vasc Anesth. 2011;25:16–9.
91. Alizadeh Ghavidel A, Totonchi Z, Chitsazan M, et al. Safety and efficacy of caproamin fides and tranexamic acid versus placebo in patients undergoing coronary artery revascularization. J Cardiovasc Thorac Res. 2014;6:197–202.
92. Choudhuri P, Biswas BK. Intraoperative use of epsilon amino caproic acid and tranexamic acid in surgeries performed under cardiopulmonary bypass: A comparative study to assess their impact on reopening due to postoperative bleeding. Ethiop J Health Sci. 2015;25:273–8.
93. Keyl C, Uhl R, Beyersdorf F, et al. High-dose tranexamic acid is related to increased risk of generalized seizures after aortic valve replacement. Eur J Cardio Thorac Surg. 2011;39:e114–21.
94. Martin K, Knorr J, Breuer T, et al. Seizures after open heart surgery: Comparison of epsilon-aminocaproic acid and tranexamic acid. J Cardiothorac Vasc Anesth. 2011;25:20–5.
95. Fergusson DA, Hébert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery [published correction appears in N Engl J Med. 2010;363:1290. N Engl J Med. 2008;358:2319–31.
96. Hutton B, Joseph L, Fergusson D, et al. Risks of harms using antifibrinolytics in cardiac surgery: Systematic review and network meta-analysis of randomised and observational studies. BMJ. 2012; 345:e5798.
97. Henry D, Carless P, Fergusson D, et al. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: A meta-analysis. CMAJ. 2009;180:183–93.
98. McIlroy DR, Myles PS, Phillips LE, et al. Antifibrinolytics in cardiac surgical patients receiving aspirin: A systematic review and meta-analysis. Br J Anaesth. 2009;102:168–78.
99. Ngaage DL, Bland JM. Lessons from aprotinin: Is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis of randomised and large matched observational studies. Eur J Cardio Thorac Surg. 2010;37:1375–83.
100. Howell N, Senanayake E, Freemantle N, et al. Putting the record straight on aprotinin as safe and effective: Results from a mixed treatment meta-analysis of trials of aprotinin. J Thorac Cardiovasc Surg. 2013;145:234–40.
101. Mansouri M, Attary M, Bagheri K, et al. Comparative evaluation of the effects of tranexamic acid and low-dose aprotinin on post-valvular heart surgery bleeding and allogenic transfusion. Interact Cardiovasc Thorac Surg. 2012;15:23–7.
102. Nejad MHG, Baharestani B, Esfandiari R, et al. Evaluation and comparison of using low-dose aprotinin and tranexamic acid in CABG: A double blind randomized clinical trial. J Tehran Heart Cent. 2012;7:15–8.
103. Riddell RE, Buth KJ, Sullivan JA. The risks associated with aprotinin use: A retrospective study of cardiac cases in Nova Scotia. Can J Anaesth. 2013;60:16–23.
104. Deloge E, Amour J, Provenchère S, et al. Aprotinin vs. tranexamic acid in isolated coronary artery bypass surgery: A multicentre observational study. Eur J Anaesthesiol. 2017;34:280–7.
105. Lewis KM, Li Q, Jones DS, et al. Development and validation of an intraoperative bleeding severity scale for use in clinical studies of hemostatic agents. Surgery. 2017;161:771–81.
106. Myles PS. Meaningful outcome measures in cardiac surgery. J Extra Corpor Technol. 2014;46:23–7.
107. Genereux P, Cohen DJ, Williams MR, et al. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: Insights from the PARTNER I trial (Placement of aortic transcatheter valve). J Am Coll Cardiol. 2014; 63:1100–9.
108. Kirmani BH, Jones SG, Malaisrie SC, et al. Limited versus full sternotomy for aortic valve replacement. Cochrane Database Syst Rev. 2017;4:CD011793.
109. Sundermann SH, Sromicki J, Rodriguez Cetina Biefer H, et al. Mitral valve surgery: Right lateral minithoracotomy or sternotomy? A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2014; 148:1989–95.e4.
110. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med. 2009;361: 1827–37.
111. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med. 2012;366: 1489–97.
112 Lamy A, Devereaux PJ, Prabhakaran D, et al. Five-year outcomes after off-pump or on-pump coronary-artery bypass grafting. N Engl J Med. 2016;375:2359–68.
113. Shroyer AL, Hattler B, Grover FL. Five-year outcomes after on-pump and off-pump coronary-artery bypass. N Engl J Med. 2017;377: 1898–9.
114. Shore-Lesserson L, Baker RA, Ferraris VA, et al. The society of thoracic surgeons, the society of cardiovascular Anesthesiologists, and the American society of ExtraCorporeal technology: Clinical practice guidelines—anticoagulation during cardiopulmonary bypass. Ann Thorac Surg. 2018;105:650–62.
115. Ak K, Isbir CS, Tetik S, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: A prospective randomized study. J Card Surg. 2009;24:404–10.
116. Shore-Lesserson L, Manspeizer HE, DePerio M, et al. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg. 1999;88:312–9.
117. Weber CF, Gorlinger K, Meininger D, et al. Point-of-care testing: A prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology. 2012;117:531–47.
118. Deppe AC, Weber C, Zimmermann J, et al. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: A meta-analysis of 8332 patients. J Surg Res. 2016;203:424–33.
119. Haas T, Fries D, Tanaka KA, et al. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: Is there any evidence? Br J Anaesth. 2015;114:217–24.
120. Toulon P, Ozier Y, Ankri A, et al. Point-of-care versus central laboratory coagulation testing during haemorrhagic surgery. A multicenter study. Thromb Haemost. 2009;101:394–401.
121. Karkouti K, McCluskey SA, Callum J, et al. Evaluation of a novel transfusion algorithm employing point-of-care coagulation assays in cardiac surgery: A retrospective cohort study with interrupted time-series analysis. Anesthesiology. 2015;122:560–70.

122. Karkouti K, Callum J, Wijeysundera DN, et al. Point-of-care hemostatic testing in cardiac surgery: A stepped-wedge clustered randomized controlled trial. Circulation. 2016;134:1152–62.
123. Afshari A, Wikkelso A, Brok J, et al. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev. 2011:CD007871.
124. Dirkmann D, Gorlinger K, Dusse F, et al. Early thromboelastometric variables reliably predict maximum clot firmness in patients undergoing cardiac surgery: A step towards earlier decision making. Acta Anaesthesiol Scand. 2013;57:594–603.
125. Corredor C, Wasowicz M, Karkouti K, et al. The role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery: A systematic review and meta-analysis. Anaesthesia. 2015;70:715–31.
126. Lodewyks C, Heinrichs J, Grocott HP, et al. Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: A systematic review and meta-analysis. Can J Anaesth. 2018;65:1333–47.
127. Groves DS, Winegar DA, Fernandez LG, et al. Comparison of coagulation parameters in arterial and venous blood in cardiac surgery measured using the Quantra system. J Cardiothorac Vasc Anesth. 2019;33:976–84.
128. Zghaibe W, Scheuermann S, Munting K, et al. Clinical utility of the Quantra((R)) point-of-care haemostasis analyser during urgent cardiac surgery. Anaesthesia. 2020;75:366–73.
129. Goldberg J, Paugh TA, Dickinson TA, et al. Greater volume of acute normovolemic hemodilution may aid in reducing blood transfusions after cardiac surgery. Ann Thorac Surg. 2015;100:1581–7; discussion 1587.
130. Stammers AH, Mongero LB, Tesdahl E, et al. The effectiveness of acute normolvolemic hemodilution and autologous prime on intraoperative blood management during cardiac surgery. Perfusion. 2017;32:454–65.
131. Zhou ZF, Jia XP, Sun K, et al. Mild volume acute normovolemic hemodilution is associated with lower intraoperative transfusion and postoperative pulmonary infection in patients undergoing cardiac surgery -- a retrospective, propensity matching study. BMC Anesthesiol. 2017;17:13.
132. Barile L, Fominskiy E, Di Tomasso N, et al. Acute normovolemic hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: A systematic review and meta-analysis of randomized trials. Anesth Analg. 2017;124:743–52.
133. Saczkowski R, Bernier PL, Tchervenkov CI, et al. Retrograde autologous priming and allogeneic blood transfusions: A meta-analysis. Interact Cardiovasc Thorac Surg. 2009;8:373–6.
134. Hofmann B, Kaufmann C, Stiller M, et al. Positive impact of retrograde autologous priming in adult patients undergoing cardiac surgery: A randomized clinical trial. J Cardiothorac Surg. 2018;13:50.
135. Cheng M, Li JQ, Wu TC, et al. Short-term effects and safety analysis of retrograde autologous blood priming for cardiopulmonary bypass in patients with cardiac valve replacement surgery. Cell Biochem Biophys. 2015;73:441–6.
136. Sun BC, Dickinson TA, Tesdahl EA, et al. The unintended consequences of over-reducing cardiopulmonary bypass circuit prime volume. Ann Thorac Surg. 2017;103:1842–8.
137 Dickinson TA, Wu X, Sturmer DL, et al. Net prime volume is associated with increased odds of blood transfusion. J Extra Corpor Technol. 2019;51:195–200.
138. Anastasiadis K, Murkin J, Antonitsis P, et al. Use of minimal invasive extracorporeal circulation in cardiac surgery: Principles, definitions and potential benefits. A position paper from the minimal invasive Extra-Corporeal Technologies international Society (MiECTiS). Interact Cardiovasc Thorac Surg. 2016;22:647–62.
139. Harling L, Warren OJ, Martin A, et al. Do miniaturized extracorporeal circuits confer significant clinical benefit without compromising safety? A meta-analysis of randomized controlled trials. ASAIO J. 2011;57:141–51.
140. Anastasiadis K, Antonitsis P, Haidich AB, et al. Use of minimal extracorporeal circulation improves outcome after heart surgery; a systematic review and meta-analysis of randomized controlled trials. Int J Cardiol. 2013;164:158–69.
141. El-Essawi A, Hajek T, Skorpil J, et al. Are minimized perfusion circuits the better heart lung machines? Final results of a prospective randomized multicentre study. Perfusion. 2011;26:470–8.
142. Anastasiadis K, Asteriou C, Antonitsis P, et al. Enhanced recovery after elective coronary revascularization surgery with minimal versus conventional extracorporeal circulation: A prospective randomized study. J Cardiothorac Vasc Anesth. 2013;27:859–64.
143. Baumbach H, Rustenbach CJ, Ahad S, et al. Minimally invasive extracorporeal bypass in minimally invasive heart valve operations: A prospective randomized trial. Ann Thorac Surg. 2016;102:93–100.
144. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. J Am Med Assoc. 2010;304:1559–67.
145. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery [published correction appears in N Engl J Med. 2015;372:2274. N Engl J Med. 2015;372:997–1008.
146. Koch CG, Sessler DI, Mascha EJ, et al. A randomized clinical trial of red blood cell transfusion triggers in cardiac surgery. Ann Thorac Surg. 2017;104:1243–50.
147. Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion. 2012;52:91–9.
148. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133–44.
149. Mueller MM, Van Remoortel H, Meybohm P, et al. Patient blood management: Recommendations from the 2018 Frankfurt consensus conference. J Am Med Assoc. 2019;321:983–97.
150. Kheiri B, Abdalla A, Osman M, et al. Restrictive versus liberal red blood cell transfusion for cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. J Thromb Thrombolysis. 2019;47:179–85.
151. Shehata N, Mistry N, da Costa BR, et al. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: A meta-analysis. Eur Heart J. 2019;40:1081–8.
152. Chen QH, Wang HL, Liu L, et al. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: A meta-analysis of randomized controlled trials. Crit Care. 2018;22:142.
153. Parke RL, McGuinness SP, Gilder E, et al. Intravenous fluid use after cardiac surgery: A multicentre, prospective, observational study. Crit Care Resusc. 2014;16:164–9.
154. Brummel-Ziedins K, Whelihan MF, Ziedins EG, et al. The resuscitative fluid you choose may potentiate bleeding. J Trauma. 2006;61:1350–8.
155. Kiraly LN, Differding JA, Enomoto TM, et al. Resuscitation with normal saline (NS) vs. lactated ringers (LR) modulates hypercoagulability and leads to increased blood loss in an uncontrolled hemorrhagic shock swine model. J Trauma. 2006;61:57–64; discussion 64–65.
156. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to plasma-Lyte. Ann Surg. 2012;255:821–9.
157. Waters JH, Gottlieb A, Schoenwald P, et al. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: An outcome study. Anesth Analg. 2001;93:817–22.
158. Zhou F, Cove ME, Peng ZY, et al. Normal saline resuscitation worsens lactic acidosis in experimental sepsis. Crit Care. 2012;16:P253.
159. Reddy SK, Bailey MJ, Beasley RW, et al. Effect of 0.9% saline or Plasma-Lyte 148 as crystalloid fluid therapy in the intensive care unit on blood product use and postoperative bleeding after cardiac surgery. J Cardiothorac Vasc Anesth. 2017;31:1630–8.
160 RobertsL, BlackhallK, AldersonP, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2011:CD001208.
161. Wigmore GJ, Anstey JR, St John A, et al. 20% human albumin solution fluid bolus administration therapy in patients after cardiac surgery (the HAS FLAIR study). J Cardiothorac Vasc Anesth. 2019;33:2920–7.

162. Skhirtladze K, Base EM, Lassnigg A, et al. Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery. Br J Anaesth. 2014;112:255–64.
163. Fink RJ, Young A, Yanez ND, et al. Cohort study of albumin versus lactated Ringer's for postoperative cardiac surgery fluid resuscitation in the intensive care unit. Pharmacotherapy. 2018;38:1241–9.
164. Rabin J, Meyenburg T, Lowery AV, et al. Restricted albumin utilization is safe and cost effective in a cardiac surgery intensive care unit. Ann Thorac Surg. 2017;104:42–8.
165. Frenette AJ, Bouchard J, Bernier P, et al. Albumin administration is associated with acute kidney injury in cardiac surgery: A propensity score analysis. Crit Care. 2014;18:602.
166. European Medicines Agency. Hydroxyethyl-Starch Solutions (HES) No Longer to be Used in Patients with Sepsis or Burn Injuries or in Critically Ill Patients. Amsterdam, Netherlands: EMA; 2018.
167. Navickis RJ, Haynes GR, Wilkes MM. Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: A meta-analysis of randomized trials. J Thorac Cardiovasc Surg. 2012;144:223–30.
168. Jacob M, Fellahi JL, Chappell D, et al. The impact of hydroxyethyl starches in cardiac surgery: A meta-analysis. Crit Care. 2014;18:656.
169. Magder S, Potter BJ, Varennes BD, et al. Fluids after cardiac surgery: A pilot study of the use of colloids versus crystalloids. Crit Care Med. 2010;38:2117–24.
170. Schramko A, Suojaranta-Ylinen R, Kuitunen A, et al. Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: A prospective randomized trial. Br J Anaesth. 2010;104:691–7.
171. Winterhalter M, Malinski P, Danzeisen O, et al. Prospective observational study for perioperative volume replacement with 6% HES 130/0,42, 4% gelatin and 6% HES 200/0,5 in cardiac surgery. Eur J Med Res. 2010;15:383–9.
172. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012; 367:1901–11.
173. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367: 124–34.
174. Vives M, Callejas R, Duque P, et al. Modern hydroxyethyl starch and acute kidney injury after cardiac surgery: A prospective multicentre cohort. Br J Anaesth. 2016;117:458–63.
175. Alavi SM, Ahmadi BB, Baharestani B, et al. Comparison of the effects of gelatin, Ringer's solution and a modern hydroxyl ethyl starch solution after coronary artery bypass graft surgery. Cardiovasc J Afr. 2012;23:428–31.
176. Datzmann T, Hoenicka M, Reinelt H, et al. Influence of 6% hydroxyethyl starch 130/0.4 versus crystalloid solution on structural renal damage markers after coronary artery bypass grafting: A post hoc subgroup analysis of a prospective trial. J Cardiothorac Vasc Anesth. 2018;32:205–11.
177. Momeni M, Nkoy Ena L, Van Dyck M, et al. The dose of hydroxyethyl starch 6% 130/0.4 for fluid therapy and the incidence of acute kidney injury after cardiac surgery: A retrospective matched study. PLoS One. 2017;12:e0186403.
178. Huang D, Chen C, Ming Y, et al. Risk of massive blood product requirement in cardiac surgery: a large retrospective study from 2 heart centers. Medicine. 2019;98:e14219.
179. Tsukinaga A, Maeda T, Takaki S, et al. Relationship between fresh frozen plasma to packed red blood cell transfusion ratio and mortality in cardiovascular surgery. J Anesth. 2018;32:539–46.
180 Tran A, Matar M, Lampron J, et al. Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2018;84:505–16.
181 Sikorski RA, Rizkalla NA, Yang WW, et al. Autologous blood salvage in the era of patient blood management. Vox Sang. 2017;112: 499–510.
182 Klein AA, Nashef SA, Sharples L, et al. A randomized controlled trial of cell salvage in routine cardiac surgery. Anesth Analg. 2008; 107:1487–95.
183 Vonk AB, Meesters MI, Garnier RP, et al. Intraoperative cell salvage is associated with reduced postoperative blood loss and transfusion requirements in cardiac surgery: A cohort study. Transfusion. 2013; 53:2782–9.
184. Paparella D, Whitlock R. Safety of salvaged blood and risk of coagulopathy in cardiac surgery. Semin Thromb Hemost. 2016;42: 166–71.

SEARCH METHODOLOGY

A limited but systematic literature search was conducted to identify key published material related to cardiac surgery and blood conservation interventions. Literature was restricted to academic articles published in English from 2009 to 2018. Seven specific questions addressed are listed, with PICOs, in Appendix A:

Peer-reviewed articles and articles were identified by searching health-related databases with international coverage (Medline via the Ovid platform and Embase via Elsevier). Where subjects are well-indexed, subject headings were used to increase relevance and precision of search results, and to ensure a manageable number of items retrieved; where subjects are less well indexed, or had not yet been assigned subject headings, key words were added to increase recall. Subject headings used were database dependent, but analogous to the Medical Subject Headings used in Medline. Search strategies are included in Appendix B.

Specific search parameters (e.g., inclusion/exclusion criteria, time frame, and language of publication) were developed in consultation with the STS researchers during initial planning stages.

Inclusion Criteria

Studies

- Secondary research: Systematic reviews, meta-analyses and other high-level evidence-based synthesis studies.
- Guidelines
- Primary research: Clinical trials and observational studies.

Jurisdictions: Any
Languages: English
Published: 2009–2018.

Exclusion Criteria

- Non-English language publications

Records from database searches were downloaded and imported into an EndNote database to facilitate removal of duplicates and screening. Final database searches were conducted during March 8–12, 2018.

Limitations

- Gray literature resources were not included for this phase of the literature search.

Items identified by database or resource type.

Database Name	Number of Items Identified*	Number of Items (Duplicates Removed)
Medline	787	786
EMbase	443	369
Total—all sources	1,230	1,155

APPENDIX A: RESEARCH QUESTIONS

Population/Intervention/Comparison/Outcome/Time.

(Provided by Scott Firestone, February 15, 2018)

1) Does preoperative dual antiplatelet therapy lead to increased perioperative bleeding in patients undergoing cardiac surgery?

Population: Adults undergoing cardiac surgery.

Intervention: Preoperative dual antiplatelet therapy.

Comparison: Aspirin only or no therapy.

Outcomes: Bleeding, and transfusion including FFP, platelets, RBCs, reexploration, mortality, and thromboembolic events.

2) Is preoperative administration of erythropoietin safe and effective in patients undergoing cardiac surgery?

P: Adults undergoing cardiac surgery.

I: Erythropoietin.

C: Erythropoietin + iron or no therapy.

O: Bleeding, and transfusion including FFP, platelets, RBCs, reexploration, mortality, and thromboembolic events.

3) Are drugs with antifibrinolytic properties safe and effective at reducing bleeding in patients undergoing cardiac surgery?

P: Adults undergoing cardiac surgery.

I: Lysine analogues, e.g., TXA and EACA.

C: No therapy.

O: Bleeding, and transfusion including FFP, platelets, RBCs, reexploration, mortality, and thromboembolic events.

4) Are novel oral anticoagulants safe and effective at reducing bleeding in patients undergoing cardiac surgery?

P: Adults undergoing cardiac surgery.

I: Novel oral anticoagulants (also direct oral anticoagulants)

C: No therapy.

O: Bleeding, and transfusion including FFP, platelets, RBCs, reexploration, mortality, and thromboembolic events.

5) Are PCCs safe and effective at reducing bleeding in patients undergoing cardiac surgery?

P: Adults undergoing cardiac surgery.

I: PCCs (e.g., KCentra)

C: No therapy.

O: Bleeding, and transfusion including FFP, platelets, RBCs, reexploration, mortality, and thromboembolic events.

6) Are restrictive transfusion strategies more effective at reducing bleeding in cardiac surgery patients than liberal strategies?

P: Adults undergoing cardiac surgery.

I: Restrictive transfusion strategies.

C: Liberal.

O: Bleeding, and transfusion including FFP, platelets, RBCs, reexploration, mortality, thromboembolic events, and dialysis.

T: Pre-, intra-, and/or postoperative.

7) Is real-time hemoglobin monitoring more effective than laboratory blood samples at reducing bleeding in cardiac surgery patients?

P: Adults undergoing cardiac surgery.

I: Real-time hemoglobin monitoring.

C: Laboratory blood samples.

O: Bleeding, and transfusion including FFP, platelets, RBCs, reexploration, mortality, and thromboembolic events.

APPENDIX B: SEARCH STRATEGIES

Ovid MEDLINE(R) Epub ahead of print, in-process, and other non-indexed citations, Ovid MEDLINE(R) daily and Ovid MEDLINE(R) < 1946 to present>.

1	exp Cardiac Surgical Procedures/	197048
2	(arterial switch operation* or arterial switch procedure* or arterial switch repair* or arterial switch technique* or double switch procedure* or double switch operation* or Rastelli operation* or Rastelli procedure* or Rastelli technique* or Rastelli repair* or Senning operation* or Senning procedure* or Senning technique* or Senning repair* or Jatene operation* or Jatene procedure* or Jatene technique* or Jatene repair* or Mustard operation* or Mustard procedure* or Mustard technique* or Mustard repair*).ti,ab.	2370
3	(valve annuloplast* or valve annular repair* or valve annular reduction* or valve annular shortening* or valve annulus repair* or valve annulus reduction* or valve annulus shortening*).ti,ab.	386
4	cardiomyoplast*.ti,ab.	841
5	(induced heart arrest or induced cardiac arrest or cardioplegia* or deep hypothermic circulatory arrest).ti,ab.	6167
6	(right heart bypass* or cavopulmonary anastomos* or cavopulmonary shunt* or Fontan operation* or Fontan procedure* or Fontan technique* or Fontan repair* or Norwood operation* or Norwood procedure* or Norwood technique* or bidirectional Glenn or bi-directional Glenn).ti,ab.	4514
7	(heart massage* or cardiac massage*).ti,ab.	1327
8	(heart transplant* or cardiac transplant* or heart graft* or cardiac graft* or heart lung transplant* or heart lung graft*).ti,ab.	29696

Continued.

9	(heart valve prosthesis implant* or aortic valve replacement*).ti,ab.	13948
10	(myocardial revascularization* or internal mammary artery implantation* or transluminal coronary balloon dilation or coronary balloon angioplast* or percutaneous transluminal coronary angioplast* or coronary artery bypass* or aortocoronary bypass* or internal mammary coronary artery anastomosis or coronary internal mammary artery anastomosis or transmyocardial laser revascularization* or laser transmyocardial revascularization* or trans myocardial laser revascularization).ti,ab.	47516
11	(pericardiectom* or pericardectom* or pericardiectom* or pericardotom* or pericardiocentes*).ti,ab.	3303
12	(heart surger* or cardiac surger* or heart surgical or cardiac surgical or heart operation* or cardiac operation*).ti,ab.	51279
13	"Surgical Procedures, Operative"/ and (exp Heart/ or (heart or cardiac or endocardium or endocardial or myocardium or myocardial or pericardium or pericardial).ti,ab.)	2735
14	Cardiovascular Surgical Procedures/	3148
15	or/1-14 [CARDIAC SURGERY]	252382
16	exp "Preoperative Period"/ or "Preoperative Care"/	62146
17	(pre-operative or preoperative or pre-operation* or preoperation* or pre-op or pre-operatively or preoperatively or presurger* or pre-surger* or presurgical* or pre-surgical* or before surger* or before surgical or preceding surger* or preceding surgical).ti,ab.	305275
18	(prior to surger* or prior to surgical or prior to operative or prior to operation* or prior to operating or preparing for surger* or preparing for surgical or preparing for operative or preparing for operation or preparing for operations).ti,ab.	17808
19	(before operative or before operation* or before operating or preceding operative or preceding operation* or preceding operating or precede operative or precede operation* or precede operating or precedes operative or precedes operative or before surger* or before surgical or preceding surger* or preceding surgical or precede surger* or precede surgical or precedes surger* or precedes surgical).ti,ab.	42399
20	(pre incision* or preincision* or before incision* or preceding incision* or precede incision* or precedes incision* or prior to incision* or preparing for incision*).ti,ab.	1177
21	(pre-procedure* or preprocedure* or before procedure* or preceding procedure* or precede procedure* or precedes procedure* or prior to procedure* or preparing for procedure*).ti,ab.	2905
22	or/16-21 [PREOP]	353643
23	(dual antiplatelet therap* or dual anti-platelet therap* or antiplatelet combination therap* or anti-platelet combination therap* or combination antiplatelet therap* or combination anti-platelet therap*).ti,ab. [Q1 INTERVENTION]	3403
24	15 and 22 and 23 [CARDIAC SURG + PREHOSP + Q1 INTERV]	71

Continued.

25	exp Erythropoietin/ or (11096-26-7 or 64FS3BFH5W or 15UQ94PT4P).rn. or (erythropoietin or "Epoetin Alfa" or Eprex or Heberitro or Procit or Binocrit or HX575 or Epogen or Darbepoetin alfa or NESP or "Novel Erythropoiesis Stimulating Protein" or "Darbepoietin alfa" or Aranesp or Aranest or " KRN 321" or KRN 321 or erythropoiesis stimulating factor or erythropoietic factor or erythropoietic stimulation factor or hematopoietin or hemopoietin).ti,ab. [Q2 INTERVENTION]	30212
26	15 and 22 and 25 [CARDIAC SURG + PREOP + Q2 INTERV]	145
27	Lysine/aa or (lysine adj6 (derivative* or analogue*)).ti,ab. or Hydroxylysine/ or 2GQB349IUB.rn. or (hydroxylysine or "2,6 Diamino 5 hydroxyhexanoic Acid").ti,ab. or Polylysine/ or 25104-18-1.rn. or (polylysine or "Poly-(Alpha-L-Lysine)").ti,ab.	13360
28	Tranexamic Acid/ or 6T84R30KC1.rn. or (AMCHA or "trans-4-(Aminomethyl)cyclohexanecarboxylic Acid" or t-AMCHA or AMCA or Anvitoff or Cyklokapron or Ugurol or KABI 2161 or Spotof or Transamin or Amchafibrin or Exacyl).ti,ab.	3033
29	Aminocaproic Acid/ or U6F3787206.rn. or (aminocaproic acid or "aminohexanoic acid" or Capralense or Capramol or Caproamin or Caprocid or Hexalense or "CY 116" or CY116 or Epsamon or Epsikapron or Hemocaprol or Amicar or Caprolest).ti,ab.	3264
30	Antifibrinolytic Agents/ or (antifibrinolyt* or antifibrinolys* or anti-fibrinolyt* or anti-fibrinolys* or plasmin inhibitor* or antiplasmin*).ti,ab.	12043
31	or/27-30 [Q3 INTERVENTION]	27975
32	15 and 31 [CARDIAC SURG + Q3 INTERV]	896
33	(novel oral anticoagulant* or novel oral anti-coagulant* or NOAC*).ti,ab.	2043
34	Dabigatran/ or I0VM4M70GC.rn. or (dabigatran or "BIBR 1048" or BIBR1048 or "BIBR 953" or "BIBR953" or Pradaxa).ti,ab.	4054
35	Rivaroxaban/ or 9NDF7JZ4M3.rn. or (rivaroxaban or Xarelto or "BAY 59-7939" or "BAY 597939").ti,ab.	3760
36	3Z9Y7UWC1J.rn. or (apixaban or " BMS 562247" or BMS562247 or eliques or eliquis).ti,ab.	2339
37	NDU3J18APO.rn. or (edoxaban or DU-176 or DU-176b or DU176 or lixiana or roteas or savaysa).ti,ab.	931
38	Factor Xa Inhibitors/ or ("factor Xa inhibitor*" or direct oral anticoagulant*).ti,ab.	5392
39	or/33-38 [Q4 INTERVENTION]	10650
40	15 and 39 [CARDIAC SURG + Q4 INTERV]	231
41	37224-63-8.rn. or (prothrombin complex concentrate* or KCentra or PPSB or cofact or "factor IX concentrate" or "factor IX complex" or Konyne or Prothromplex-Immuno or Proplex or Prothrombinex or Autoplex-T or Octaplex or beriplex or cofact or confidex or kaskadil or kedcom or ocplex or prothrombin complex preparation* or prothrombin converting complex or prothrombin converting enzyme or uman complex).ti,ab. [Q5 INTERVENTION]	2102
42	15 and 41 [CARDIAC SURG + Q5 INTERV]	103
43	((restrictive or conservative) adj3 transfus* adj3 strateg*).ti,ab.	210

Continued.

44	exp Blood Transfusion/ and (restrictive or conservative).ti,ab.	913
45	43 or 44 [Q6 INTERVENTION]	974
46	15 and 45 [CARDIAC SURG + Q6 INTERV]	91
47	("real time" and (monitor* or measur* or assess*)).ti,ab. and (Hemoglobins/ or (hemoglobin* or haemoglobin* or Hb).ti,ab.) [Q7 INTERVENTION]	746
48	15 and 47 [CARDIAC SURG + Q7 INTERV]	15
49	("Blood Loss, Surgical"/ or ((surgical or surger* or operative) adj3 ("blood loss" or bleeding or hemorrhag* or haemorrhag*)).ti,ab.) adj3 (prevent* or manag* or control*).ti,ab.	1019
50	("blood management" or "blood conservation").ti,ab.	1495
51	49 or 50 [GENERAL INTERV]	2497
52	15 and 51 [CARDIAC SURG + GENERAL INTERV]	489
53	or/24,26,32,40,42,46,48,52	1897
54	limit 53 to (english language and yr="2009 -Current")	881
55	(Animals/ or Animal Experimentation/ or "Models, Animal"/ or (animal* or nonhuman* or non human* or rat or rats or mouse or mice or rabbit or rabbit or pig or pigs or porcine or dog or dogs or hamster or hamsters or fish or chicken or chickens or sheep or cat or cats or raccoon or raccoons or rodent* or horse or horses or racehorse or racehorses or beagle*).ti,ab.) not (Humans/ or (human* or participant* or patient or patients or child* or seniors or adult or adults).ti,ab.)	4118132
56	(editorial or comment or letter or newspaper article).pt.	1630143
57	(conference or conference abstract or conference paper or "conference review" or congresses).pt.	64438
58	54 not (55 or 56 or 57)	790
59	remove duplicates from 58	787

Elsevier Embase 1947 to Present.

1	'heart surgery'/exp	342,324
2	'arterial switch operation*':ti,ab OR 'arterial switch procedure*':ti,ab OR 'arterial switch repair*':ti,ab OR 'arterial switch technique*':ti,ab OR 'double switch procedure*':ti,ab OR 'double switch operation*':ti,ab OR 'rastelli operation*':ti,ab OR 'rastelli procedure*':ti,ab OR 'rastelli technique*':ti,ab OR 'rastelli repair*':ti,ab OR 'senning operation*':ti,ab OR 'senning procedure*':ti,ab OR 'senning technique*':ti,ab OR 'senning repair*':ti,ab OR 'jatene operation*':ti,ab OR 'jatene procedure*':ti,ab OR 'jatene technique*':ti,ab OR 'jatene repair*':ti,ab OR 'mustard operation*':ti,ab OR 'mustard procedure*':ti,ab OR 'mustard technique*':ti,ab OR 'mustard repair*':ti,ab	3,236
3	'valve annuloplast*':ti,ab OR 'valve annular repair*':ti,ab OR 'valve annular reduction*':ti,ab OR 'valve annular shortening*':ti,ab OR 'valve annulus repair*':ti,ab OR 'valve annulus reduction*':ti,ab OR 'valve annulus shortening*':ti,ab	573
4	cardiomyoplast*:ti,ab	988
5	'induced heart arrest':ti,ab OR 'induced cardiac arrest':ti,ab OR 'cardioplegia*':ti,ab OR 'deep hypothermic circulatory arrest':ti,ab	7,742
6	'right heart bypass*':ti,ab OR 'cavopulmonary anastomos*':ti,ab OR 'cavopulmonary shunt*':ti,ab OR 'fontan operation*':ti,ab OR 'fontan procedure*':ti,ab OR 'fontan technique*':ti,ab OR 'fontan repair*':ti,ab OR 'norwood operation*':ti,ab OR 'norwood procedure*':ti,ab OR 'norwood technique*':ti,ab OR 'bidirectional glenn':ti,ab OR 'bi-directional glenn':ti,ab	6,192

Continued.

7	'heart massage*':ti,ab OR 'cardiac massage*':ti,ab	2,271
8	'heart transplant*':ti,ab OR 'cardiac transplant*':ti,ab OR 'heart graft*':ti,ab OR 'cardiac graft*':ti,ab OR 'heart lung transplant*':ti,ab OR 'heart lung graft*':ti,ab	44,859
9	'heart valve prosthesis implantat*':ti,ab OR 'aortic valve replacement*':ti,ab	20,833
10	'myocardial revascularization*':ti,ab OR 'internal mammary artery implantation*':ti,ab OR 'transluminal coronary balloon dilation':ti,ab OR 'coronary balloon angioplast*':ti,ab OR 'percutaneous transluminal coronary angioplast*':ti,ab OR 'coronary artery bypass*':ti,ab OR 'aortocoronary bypass*':ti,ab OR 'internal mammary coronary artery anastomosis':ti,ab OR 'coronary internal mammary artery anastomosis':ti,ab OR 'transmyocardial laser revascularization*':ti,ab OR 'laser transmyocardial revascularization*':ti,ab OR 'trans myocardial laser revascularization':ti,ab	60,249
11	pericardectom*:ti,ab OR pericardiectom*:ti,ab OR pericardotom*:ti,ab OR pericardiocentes*:ti,ab	5,140
12	'heart surger*':ti,ab OR 'cardiac surger*':ti,ab OR 'heart surgical':ti,ab OR 'cardiac surgical':ti,ab OR 'heart operation*':ti,ab OR 'cardiac operation*':ti,ab	72,891
13	'surgery'/de AND ('heart'/de OR heart:ti,ab OR cardiac:ti,ab OR endocardium:ti,ab OR endocardial:ti,ab OR myocardium:ti,ab OR myocardial:ti,ab OR pericardium:ti,ab OR pericardial:ti,ab)	49,303
14	'cardiovascular surgery'/de	12,203
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	419,707
16	'preoperative period'/exp OR 'preoperative care'/de OR 'preoperative treatment'/de	270,021
17	'pre-operative':ti,ab OR 'preoperative':ti,ab OR 'pre-operation*':ti,ab OR 'preoperation*':ti,ab OR 'pre-op':ti,ab OR 'pre-operatively':ti,ab OR 'preoperatively':ti,ab OR 'presurger*':ti,ab OR 'pre-surger*':ti,ab OR 'presurgical*':ti,ab OR 'pre-surgical*':ti,ab OR 'before surger*':ti,ab OR 'before surgical':ti,ab OR 'preceding surger*':ti,ab OR 'preceding surgical':ti,ab	436,301
18	'prior to surger*':ti,ab OR 'prior to surgical':ti,ab OR 'prior to operative':ti,ab OR 'prior to operation*':ti,ab OR 'prior to operating':ti,ab OR 'preparing for surger*':ti,ab OR 'preparing for surgical':ti,ab OR 'preparing for operative':ti,ab OR 'preparing for operation':ti,ab OR 'preparing for operations':ti,ab	22,596
19	'before operative':ti,ab OR 'before operation*':ti,ab OR 'before operating':ti,ab OR 'preceding operative':ti,ab OR 'preceding operation*':ti,ab OR 'preceding operating':ti,ab OR 'precede operative':ti,ab OR 'precede operation*':ti,ab OR 'precede operating':ti,ab OR 'precedes operative':ti,ab OR 'before surger*':ti,ab OR 'before surgical':ti,ab OR 'preceding surger*':ti,ab OR 'preceding surgical':ti,ab OR 'precede surger*':ti,ab OR 'precede surgical':ti,ab OR 'precedes surger*':ti,ab OR 'precedes surgical':ti,ab	62,442
20	'pre incision*':ti,ab OR 'preincision*':ti,ab OR 'before incision*':ti,ab OR 'preceding incision*':ti,ab OR 'precede incision*':ti,ab OR 'precedes incision*':ti,ab OR 'prior to incision*':ti,ab OR 'preparing for incision*':ti,ab	1,527
21	'pre-procedure*':ti,ab OR 'preprocedure*':ti,ab OR 'before procedure*':ti,ab OR 'preceding procedure*':ti,ab OR 'precede procedure*':ti,ab OR 'precedes procedure*':ti,ab OR 'prior to procedure*':ti,ab OR 'preparing for procedure*':ti,ab	5,662

Continued.

22	#17 OR #18 OR #19 OR #20 OR #21	466,699
23	'dual antiplatelet therapy'/de OR 'dual antiplatelet therap*':ti,ab OR 'dual anti-platelet therap*':ti,ab OR 'antiplatelet combination therap*':ti,ab OR 'anti-platelet combination therap*':ti,ab OR 'combination antiplatelet therap*':ti,ab OR 'combination anti-platelet therap*':ti,ab	7,826
24	#15 AND #22 AND #23	134
25	'erythropoietin'/exp OR '11096 26 7':rn OR 64fs3bfh5w: rn OR 15uq94pt4p:rn OR 'erythropoietin':ti,ab OR 'epoetin alfa':ti,ab OR 'eprex':ti,ab OR 'heberitro': ti,ab OR 'procit':ti,ab OR 'binocrit':ti,ab OR 'hx575': ti,ab OR 'epogen':ti,ab OR 'darbepoetin alfa':ti,ab OR 'nesp':ti,ab OR 'novel erythropoiesis stimulating protein':ti,ab OR 'darbepoietin alfa':ti,ab OR 'aranesp':ti,ab OR 'aranest':ti,ab OR 'krn 321':ti,ab OR 'erythropoiesis stimulating factor':ti,ab OR 'erythropoietic factor':ti,ab OR 'erythropoietic stimulation factor':ti,ab OR 'hematopoietin':ti,ab OR 'hemopoietin':ti,ab	47,472
26	#15 AND #22 AND #25	223
27	'lysine'/de AND (analog:ti,ab OR analogs:ti,ab OR analogue*:ti,ab OR derivative*:ti,ab) OR ((lysine NEAR/6 (analog OR analogs OR analogue* OR derivative*)):ti,ab) OR '6 (gamma glutamyl)lysine'/de OR 'hydroxylysine'/de OR 2gqb349iub:rn OR hydroxylysine:ti,ab OR '2,6 diamino 5 hydroxyhexanoic acid':ti,ab OR 'polylysine'/de OR '25104-18-1':rn OR polylysine:ti,ab OR 'poly-(alpha-l-lysine)':ti,ab	14,889
28	'tranexamic acid'/de OR '6t84r30kc1':rn OR amcha:ti,ab OR 'trans-4-(aminomethyl)cyclohexanecarboxylic acid':ti,ab OR 't-amcha':ti,ab OR amca:ti,ab OR anvitoff:ti,ab OR cyklokapron:ti,ab OR ugurol:ti,ab OR 'kabi 2161':ti,ab OR spotof:ti,ab OR transamin: ti,ab OR amchafibrin:ti,ab OR exacyl:ti,ab	10,974
29	'aminocaproic acid'/de OR 'u6f3787206':rn OR 'aminocaproic acid':ti,ab OR 'aminohexanoic acid': ti,ab OR capralense:ti,ab OR capramol:ti,ab OR caproamin:ti,ab OR caprocid:ti,ab OR hexalense:ti,ab OR 'cy 116':ti,ab OR cy116:ti,ab OR epsamon:ti,ab OR epsikapron:ti,ab OR hemocaprol:ti,ab OR amicar:ti,ab OR caprolest:ti,ab	8,025
30	'antifibrinolytic agents'/de OR antifibrinolyt*:ti,ab OR antifibrinolys*:ti,ab OR 'anti-fibrinolyt*':ti,ab OR 'anti-fibrinolys*':ti,ab OR 'plasmin inhibitor*':ti,ab OR antiplasmin*:ti,ab	12,406
31	#27 OR #28 OR #29 OR #30	40,511
32	#15 AND #31	2,230
33	'novel oral anticoagulant*':ti,ab OR 'novel oral anti-coagulant*':ti,ab OR noac*:ti,ab	4,049
34	'dabigatran'/de OR 'i0vm4m70gc':rn OR dabigatran: ti,ab OR 'bibr 1048':ti,ab OR bibr1048:ti,ab OR 'bibr 953':ti,ab OR 'bibr953':ti,ab OR pradaxa:ti,ab	11,166
35	'rivaroxaban'/de OR '9ndf7jz4m3':rn OR rivaroxaban: ti,ab OR xarelto:ti,ab OR 'bay 59-7939':ti,ab OR 'bay 597939':ti,ab	11,728
36	'3z9y7uwc1j':rn OR apixaban:ti,ab OR 'bms 562247':ti,ab OR bms562247:ti,ab OR eliques:ti,ab OR eliquis:ti,ab	4,068
37	(ndu3j18apo:rn OR edoxaban:ti,ab OR 'du-176':ti,ab OR 'du-176b':ti,ab OR du176:ti,ab OR lixiana:ti,ab OR roteas:ti,ab OR savaysa:ti,ab) AND 'factor xa inhibitors'/de OR 'factor xa inhibitor*':ti,ab OR 'direct oral anticoagulant*':ti,ab	4,720
38	'factor xa inhibitors'/de OR 'factor xa inhibitor*':ti,ab OR 'direct oral anticoagulant*':ti,ab	6,742
39	#33 OR #34 OR #35 OR #36 OR #37 OR #38	21,928
40	#15 AND #39	1,418
41	'37224-63-8':rn OR 'prothrombin complex concentrate*':ti,ab OR kcentra:ti,ab OR ppsb:ti,ab OR 'factor ix concentrate':ti,ab OR 'factor ix complex':ti,ab OR konyne:ti,ab OR 'prothromplex-immuno':ti,ab OR proplex:ti,ab OR prothrombinex: ti,ab OR 'autoplex-t':ti,ab OR octaplex:ti,ab OR beriplex:ti,ab OR cofact:ti,ab OR confidex:ti,ab OR kaskadil:ti,ab OR kedcom:ti,ab OR ocplex:ti,ab OR 'prothrombin complex preparation*':ti,ab OR 'prothrombin converting complex':ti,ab OR 'prothrombin converting enzyme':ti,ab OR 'uman complex':ti,ab	5,012
42	#15 AND #41	411
43	((restrictive OR conservative) NEAR/3 transfus* NEAR/3 strateg*):ti,ab	365
44	'blood transfusion'/exp AND (restrictive:ti,ab OR conservative:ti,ab)	2,749
45	#43 OR #44	2,807
46	#15 AND #45	253
47	'real time':ti,ab AND (monitor*:ti,ab OR measur*:ti,ab OR assess*:ti,ab) AND ('hemoglobins'/de OR hemoglobin*: ti,ab OR haemoglobin*:ti,ab OR hb:ti,ab)	1,361
48	#15 AND #47	40
49	('blood loss, surgical'/de OR (((surgical OR surger* OR operative) NEAR/3 ('blood loss' OR bleeding OR hemorrhag* OR haemorrhag*)):ti,ab)) AND (prevent*:ti,ab OR manag*:ti,ab OR control*:ti,ab)	15,800
50	'blood management':ti,ab OR 'blood conservation':ti,ab	2,520
51	#49 OR #50	18,076
52	#15 AND #51	2,100
53	#24 OR #26 OR #32 OR #40 OR #42 OR #46 OR #48	4,447
54	#53 AND [english]/lim AND [2009-2017]/py	2,934
55	'animal'/de OR 'animal experiment'/de OR 'animal model'/de OR ((animal*:ti,ab OR nonhuman*:ti,ab OR 'non human*':ti,ab OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR rabbit:ti,ab OR pig: ti,ab OR pigs:ti,ab OR porcine:ti,ab OR dog:ti,ab OR dogs:ti,ab OR hamster:ti,ab OR hamsters:ti,ab OR fish:ti,ab OR chicken:ti,ab OR chickens:ti,ab OR sheep:ti,ab OR cat:ti,ab OR cats:ti,ab OR raccoon: ti,ab OR raccoons:ti,ab OR rodent*:ti,ab OR horse: ti,ab OR horses:ti,ab OR racehorse:ti,ab OR racehorses:ti,ab OR beagle*:ti,ab) NOT ('human'/de OR human*:ti,ab OR participant*:ti,ab OR patient: ti,ab OR patients:ti,ab OR child*:ti,ab OR seniors: ti,ab OR adult:ti,ab OR adults:ti,ab))	5,361,027
56	'conference abstract':it OR editorial:it OR letter:it OR note:it	5,169,661
57	#54 NOT (#55 OR #56)	1,726
58	#57 AND [embase]/lim NOT [medline]/lim	443