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

Pierre Tibi, MD[1]
R. Scott McClure, MD SM FRCSC[2]
Jiapeng Huang, MD[3]
Robert A. Baker, PhD, CCP[4]
David Fitzgerald, DHA, CCP[5]
C. David Mazer, MD[6]
Marc Stone, MD[7]
Danny Chu, MD[8]
Alfred H. Stammers, MSA, PBMS, CCP Emeritus[9]
Tim Dickinson, CCP[10]
Linda Shore-Lesserson, MD[11]
Victor Ferraris, MD[12]
Scott Firestone[13]
Kalie Kissoon[13]
Susan Moffatt-Bruce, MD[14]

[1] Department of Cardiovascular Surgery, Yavapai Regional Medical Center, Prescott, AZ
[2] Division of Cardiac Surgery, Libin Cardiovascular Institute, Foothills Medical Center, University of Calgary, Calgary, Alberta, Canada
[3] Department of Anesthesiology & Perioperative Medicine, University of Louisville, Louisville, KY
[4] Cardiac Surgery Research and Perfusion, Flinders University and Flinders Medical Centre, Adelaide, South Australia, Australia
[5] Division of Cardiovascular Perfusion, Medical University of South Carolina, Charleston, SC
[6] Department of Anesthesia, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[7] Department of Anesthesia, Mount Sinai Medical Center, New York, NY
[8] Department of Cardiothoracic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
[9] Specialty Care, Nashville, TN
[10] Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN
[11] Department of Anesthesiology, Zucker School of Medicine at Hofstra/Northwell Northshore University Hospital, Manhasset, NY
[12] Division of Cardiovascular and Thoracic Surgery, University of Kentucky, Lexington, KY
[13] The Society of Thoracic Surgeons, Chicago, IL
[14] Division of Thoracic Surgery, The Ohio State University Medical Center, Columbus, OH

Executive Summary

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

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

As standards for developing clinical practice guidelines have themselves evolved since 2011, the authors were tasked with prioritizing topics for systematic review, while still aiming for the comprehensive approach from previous versions of this manuscript. These high-priority systematically-reviewed topics make up the bulk of this manuscript, and resulted in 23 new or updated recommendations for 2020. Additionally, all previous recommendations not directly addressed by a systematic review, were voted on by consensus for inclusion in the 2020 update. Together, these recommendations address the full spectrum of care for patients undergoing cardiac surgery, while being streamlined to include only the most clinically-relevant interventions.

Introduction

Blood transfusion is a critical and life-saving facet of the care for cardiothoracic surgery patients. Inherent to the transfusing of blood, is the understanding of the preservation of blood as well as the appropriateness of techniques to prevent hemorrhage through the clinical course. Although clinical practices have evolved through the centuries since Dr. William Harvey discovered the circulation of blood in 1628 and attempted the first blood transfusion thereafter, there is significant variability in the practices of blood transfusion and conservation in all phases of the surgical care. In our current healthcare environment of value-based care, the need for practice guidelines must therefore be further emphasized. Additionally, the term "blood conservation" is yielding to a broader term "Patient Blood Management" (PBM) that incorporates the need to not only "conserve" blood but more importantly 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 multi-disciplinary 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 in order to achieve improved patient outcomes. Surgical outcomes are now being held to a higher standard and sharing of outcomes, often in very public forums, is the new normal. Additionally, resource utilization and efficient care has to be foundational to our provision of care for every cardiothoracic surgery patient. High value care with excellent outcomes by using the appropriate resources is now at the forefront of healthcare delivery.

This was a collective project of STS, SCA, AmSECT and SABM to review the current literature, revise previous guidelines and develop a series of practice guidelines that reflect the current evidence and practice portfolios that are used in cardiothoracic surgery in North America. Critical to this review and guideline development was an understanding of the patient care paradigm throughout the care

continuum. The care continuum consisted of exploring the informed consent process, preoperative conditioning, the current clinical use of antiplatelet agents and preoperative anticoagulants, intraoperative blood management (including intravenous and topic hemostatic agent use) and the post-operative management of patients undergoing cardiopulmonary bypass. 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 guidelines, that are practical and will be received as being reasonable and well- researched. While we have collectively tried to accumulate the evidence and data from a broad number of stakeholders and sources, we recognize that it may be impossible to have every data point. Our intent is to present the most comprehensive set of guidelines possible and we hope that this will serve as a resource so to improve the outcomes of patients undergoing cardiothoracic surgery.

Methodology

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

The members of the writing committee submitted conflict of interest disclosure forms, which were reviewed by the Chair and STS staff prior to 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, 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 PCI or another type of surgery aside from cardiac), or the primary outcomes were secondary markers with uncertain relationship to the hard clinical outcomes selected by the writing committee.

Two authors (SF, KK) developed an evidence table of the relevant papers (Appendix 2) and rated the studies for risk of bias. The Newcastle-Ottawa scale was used for observational studies (Appendix 3), and a custom-made checklist was used for randomized control trials (RCTs) and meta-analyses (Appendix 4). The bulk of the manuscript is focused on the results of this systematic review. Recommendations from previous versions of this manuscript 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 manuscript, but which were maintained in this version due to having continued clinical relevance are included in Table 1. All current and valid recommendations are categorized and presented in Table 2. Voting on recommendations utilized 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 ACC/AHA Classification System (Appendix 6).

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

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

Table 1. Updated Recommendations from Previous Guidelines Which Are Not a Focus of the Manuscript

Intervention	ACC/AHA Class and Level
Preoperative identification of high-risk patients should be performed, and all available preoperative and perioperative measures of blood conservation should be undertaken in this group as they account for the majority of blood products transfused.	Class I, Level A
In purely elective patients without acute coronary syndromes, it is reasonable to discontinue low-intensity antiplatelet drugs (e.g., aspirin) before surgery with the expectation that blood transfusion will be reduced.	Class IIA, Level A
Minimization of phlebotomy through a reduction in blood sampling volumes and frequencies is a reasonable means of blood conservation.	Class IIA, Level B-NR
The very early addition of a P2Y12 inhibitor to aspirin therapy in the postoperative care of coronary artery bypass grafting patients prior to ensuring surgical hemostasis may increase bleeding and the need for surgical re-exploration, and is not recommended.	Class III: No Benefit, Level C-LD
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's 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
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 cardiopulmonary bypass.	Class I, Level A
In high-risk patients with known malignancy who require CPB, blood salvage using centrifugation of salvaged blood from the operative field may be considered when allogeneic transfusion is required.	Class IIB, Level B-NR
Centrifugation of pump-salvaged blood is reasonable for minimizing post-CPB allogeneic red blood cell (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
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
Routine use of red cell salvage using centrifugation is helpful for blood conservation in cardiac operations using CPB.	Class I, Level A
Direct reinfusion of shed mediastinal blood from postoperative chest tube drainage is not recommended as a means of blood conservation and may cause harm.	Class III: Harm, Level B-NR
A comprehensive multimodality blood conservation program led by a multidisciplinary team of health care providers should be part of any Patient Blood Management program to limit utilization of blood resources and decrease the risk of bleeding.	Class I, Level B-R

139

140

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-NR)**

It is well known from the original 2007 STS Blood Conservation Guidelines that preoperative preparation of patients with regard to blood utilization in cardiac surgery, when feasible, is of the utmost importance for consistent blood conservation strategies. Identification of high risk individuals whether it be from advanced age, preoperative anemia or abnormal coagulation profiles is a Class 1 intervention. Additionally, one of the most significant determinants of patients needing perioperative transfusions is preoperative anemia. Anemia is extremely prevalent in the cardiac surgical population, especially in elderly patients or patients with multiple comorbidities and chronic diseases. Recent studies identify the prevalence of anemia in the 30-40% range (1,2) and severe anemia by WHO classification of Hb < 8g/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 prior to surgery. Differentiation must be made between anemias caused by iron deficiency as opposed to other causes of anemia. Iron deficiency anemia is usually microcytic while normocytic or macrocytic anemia stem from a variety of causes. Routine iron studies are of importance in the determination of the type of anemia present and should be done routinely in the careful preoperative assessment of patients so that treatment can be instituted if warranted.

There is a distinct correlation between preoperative anemia and worse clinical outcomes in most studies. Usually, the greater the anemia, the more severe the complications. In a prospective observational study of over 200 patients undergoing coronary artery bypass graft (CABG) surgery, preoperative hematocrit remained an independent predictor for major morbidity (OR = 0.95, p = 0.01), while transfusion was also a strong predictor (OR = 4.86, p < 0.001) (5). Multiple recent retrospective studies demonstrate higher morbidity and mortality in patients with preoperative anemia although some only show an association with long term mortality. Additionally, there appears to be a cumulative effect of anemia and transfusions that increase risks. In comparisons of patients undergoing CABG surgery that were transfused as opposed to not transfused, there was greater mortality in the transfused patients. (11% vs. 5.3%; p=0.001). Patients with anemia who were transfused had a hazard rate for mortality three times higher than nonanemic patients who did not receive transfusion (HR: 2.918, 95% confidence interval 1.512 - 5.633, p=0.001), and twice that of anemic patients who were not transfused (HR: 2.087, 95% confidence interval 1.004 - 4.336, p=0.049) (6). Preoperative anemia has also been associated with increased transfusion rates and longer ICU and hospital lengths of stay (1) and an increase in acute kidney injury (AKI) (7). However, in one retrospective study, only normocytic or macrocytic anemia was associated with increased adverse events (8).

Preoperative Treatment of Anemia – Pharmacological Agents

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

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

inconvenience, cost and/or refusal to pay for iron and erythropoietin therapy by insurers and the oftentimes overstated risks of these therapies. Nevertheless, treatment of an anemic patient prior to 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 prior to 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 randomized controlled trial of only 50 patients did not (10). Therefore, it is difficult to confidently state that the direct treatment of iron deficiency anemia prior to 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. Erythropoietin 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 utilizing 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 control group; $p = 0.001$). Likewise, a prospective observational study by Cladellas et al of ESAs and iron showed a reduction in the rate of transfused patients (67% vs. 93% in the control group; $p < 0.001$) and 30 day mortality (multivariable OR: 0.16, [95% CI, 0.28-0.97] $p = 0.04$) (11).

There is enough evidence to state that the non-anemic 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, 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 one to two weeks.

Recombinant human erythropoietin 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 (12,13). Additionally, there are several randomized controlled trials that have shown a nephroprotective effect of preoperative treatment on anemic patients with ESAs only (14-16).

Other considerations for the use of ESAs include situations in which endogenous EPO production is limited. For instance, beta-blockers suppress endogenous EPO production (17), and perioperative anemia decreases the cardioprotective effect of betablockade (18). Additionally, cytokines stimulated by the inflammatory response associated with CPB limit production of EPO (19). Perioperative renal ischemia may limit the production of EPO. Likewise, careful postoperative management may improve tissue oxygen delivery and suppress endogenous EPO production despite postoperative anemia. Decreased perioperative EPO production favors a short preoperative course of ESA (a few days before operation) to treat reduced RBC volume in selected individual patients.

In a prospective randomized controlled trial of 600 anemic patients, a single dose of 80,000 u of epoetin alfa given to patients 2 days prior to surgery resulted in significantly lower postoperative transfusion rates (17% vs. 39%; RR: 0.436, $p < 0.0005$) and higher HgB on day 4 post surgery (10.2 % vs. 8.7%; $p < 0.0005$), although no significant differences in mortality and adverse events at 45 days (20). A second randomized trial of 320 patients who had a variety of cardiac procedures done off-pump also resulted in

fewer RBC transfusions (37.1% vs. 16.1%, RR: 0.425; p = 0.007) without a significant difference in adverse events, although this study required four times as many patients to detect such a difference (21). 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 pre vs. perioperative EPO and patients at lower risk for cardiac surgery associated acute kidney injury (22).

It has been suggested that a short-term combination therapy with IV iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid may provide reduced risk of transfusion in anemic patients having cardiac procedures (23). This observation needs further investigation before broad-based acceptance can be recommended.

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

Preoperative Diagnosis and Treatment of Anemia – Non-pharmacologic Interventions

- **In patients undergoing cardiac operations, it is reasonable to implement standardized transfusion protocols in order to reduce transfusion burden. (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)**

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 (24).

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 (Figure 1) (25). 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, (26-28) but there is conflicting evidence that preoperative transfusion to higher hemoglobin levels impacted this risk (26,29,30). 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 (31).

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

Use of preoperative autologous blood donation (PABD) is a theoretically rational approach for patients having elective cardiac procedures using CPB. While there has been a slight uptick in the number of autologous blood donations in recent years (2015-2017), it still remains a fraction (<1%) of total collected RBCs (32). 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 (33).

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 FFP transfusion without additional transfusion-related side effects (34). 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 (35). There is currently insufficient data to make a definitive recommendation on the practice of PABD in cardiac surgery.

There is good observational data to suggest that a standardized protocol for evidence-based blood product transfusion and blood conservation in the perioperative setting favors improved clinical outcomes in routine cardiac procedures. A propensity matched analysis suggested that 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 (36).

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 (37,38). These rights are rooted in the fundamental principles of clinical/legal ethics; autonomy, veracity, beneficence, non-maleficence and justice (39).

Designation of decision-making capacity at a certain age is an arbitrary but necessary legal distinction. In the case of unemancipated patients under the age of eighteen, 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 transfuse an unemancipated patient who is younger than eighteen years of age 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 (40). In a non-emergency 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/her clinical condition. Jehovah's Witnesses refuse certain aspects of hemotherapy. Proscribed blood components are red cells, leukocytes, platelets and plasma. In general the remainder of hemotherapies are left to the conscience of the individual Witness to decide (41,42).

See table below.

Blood Products and Procedures Examples of Variability in Acceptance Among JWs	
Not Acceptable	**May Be Acceptable**
Blood, Blood Products and Blood Fractions	
Whole blood	**Recombinant Products such as G-CSF, Epo, Coagulation factors**
Red Cells	**Albumin**
White Cells	**Coagulation Factors**
Platelets	**Cryoprecipitate**

Fresh Frozen Plasma (FFP)	**Hemoglobin**
Autologous Pre-donation	**Hemin**
	Immunoglobulin
Therapeutic Procedures Involving Patient's Own Blood	
Autologous Pre-donation & Reinfusion	**Cell Salvage**
	Hemodilution
	Extracorporeal blood re-circulation
	Dialysis
	Platelet Gel-Autologous
	Labeling or Tagging

317

318

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

324

325 Admittedly, PBM should be practiced in all patients regardless of their personal beliefs. Nevertheless
326 there are multiple nuances that must be considered and specifically addressed in Jehovah Witnesses
327 such as the consensual use of cell salvage, ANH and other modalities. The consent process requires
328 these issues to be discussed and agreed upon and, bear in mind, informed consent implies the ability to
329 give informed refusal (43).

330

331 ## Preoperative Anticoagulants

- **In patients in need of emergent cardiac surgery with recent ingestion of a non-vitamin 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 alfa for either apixaban or rivaroxaban at appropriate dose). (Class IIA, Level C-LD)**
- **If the antidote for the specified NOAC is not available, prothrombin concentrate is recommended, recognizing that the effective response may be variable. (Class IIA, Level C-LD)**
- **Prothrombin concentrate is reasonable to consider over fresh frozen plasma as first line therapy for refractory coagulopathy in cardiac surgery in select situations to reduce bleeding. (Class IIA, Level B-R)**

Most aspects of the contemporary anticoagulation management strategies in the preoperative preparatory phase for cardiac surgical patients (so as 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 (44,45) about which the cardiac surgical teams needs to be knowledgeable, as 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 non-valvular atrial fibrillation as well as to treat venous thromboembolism (46-49). 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 surgeries with a high risk bleeding profile. Available measurement assays to assess anticoagulation for NOACs are imprecise and the availability of reversal agents is limited (50-52). Given the predictable and rather short half-life to NOACs, in the elective setting, discontinuation for

at least 2 days prior to surgery is recommended, though renal impairment will require extending this discontinuation for additional days in select situations (53,54). 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 prior to elective cardiac surgery (55,56).

A prior concern with NOACs was the limited availability of reversal agents. Going forward this will be less of a concern as the US Food and Drug Administration have recently approved antidotes for the more widely utilized NOACs. For dabigatran, idarucizumab, a human monoclonal anti-dabigatran antibody is now available. And for apixaban and rivaroxaban, the modified recombinant factor Xa, andexanet alfa, is available (57). In situations where these antidotes are not readily available, prothrombin complex concentrates (PCC) may prove beneficial and are recommended, though efficacy may vary (54). As well, though not widely available, point-of-care (POC) testing with either thrombin clotting time for dabigatran or anti-factor Xa assays for apixaban and rivaroxaban can aid in determining anticoagulant effect of these NOACs at the time of emergent surgery (50-52). The use of these laboratory tests is recommended if readily available.

Beyond being a non-specific antidote to NOACs in emergent situations, the safety and effectiveness of PCC to reduce bleeding in cardiac surgery has been further evaluated since the 2011 guidelines. Already the preferred therapy for emergent warfarin reversal (58), PCC may also be applicable in cases of refractory bleeding (59). Prothrombin complex concentrates facilitate rapid correction of vitamin K dependent coagulation factors without the potential deleterious effects of volume overload attributed to fresh frozen plasma (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, which included two analyses: a propensity-score adjusted multivariate analysis of 971 patients, and

propensity-score matched cohorts of 225 pairs using PCC or FFP for first line therapy in coagulopathy showed a decrease in postoperative blood loss and blood transfusions. However, in the multivariate analysis, this was at the expense of increased acute kidney injury (AKI) and renal replacement therapy (RRT). These differences were not confirmed in the analysis of the matched pairs (60). There was no difference in thromboembolic events.

A meta-analysis of observational studies with 861 patients, including those in the aforementioned propensity-matched analysis, also showed decreased postoperative blood loss and blood transfusions with PCC at varying doses. There was no difference in thromboembolic events and no difference in AKI. Noteworthy, there was a non-significant trend toward increased RRT in the pooled outcome, although the relatively wide confidence interval suggests a fair amount of uncertainty (OR: 0.41, 95% CI, 0.16 – 1.02; p = 0.06). Hospital mortality and re-exploration were likewise not statistically significant (61).

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

Antiplatelets

- **In order to reduce bleeding in patients requiring elective cardiac surgery, ticagrelor should be withdrawn preoperatively for a minimum of 3 days, clopidogrel for 5 days and prasugrel for 7 days. (Class I, Level B-NR)**

- **Laboratory and/or point-of-care measurement of antiplatelet drug effect in patients having received recent dual antiplatelet therapy can be useful to assess bleeding risk or to guide timing of surgery. (Class IIA, Level B-R)**

Dual antiplatelet therapy (DAPT) with a P2Y12 inhibitor and aspirin is well-demonstrated to decrease ischemic risk and thrombotic complications in patients with acute coronary syndromes (ACS) and following percutaneous coronary intervention (PCI) when compared to single antiplatelet therapy (SAPT) with aspirin alone (62-66). 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., coronary artery bypass grafting; CABG) increases intra- and perioperative bleeding, rates of transfusion of blood and blood products (especially platelets) and postoperative re-exploration for mediastinal bleeding (67-73). Thus, for ACS patients requiring surgical intervention, where feasible, preoperative cessation of the P2Y12 inhibitor has been recommended in previous American and European guidelines (58,74,75).

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 (76,77). The results of point-of-care 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 employed 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 (78), as well as inter-individual variability in antiplatelet effect. Thus, the optimal minimum timeframe(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 below. Further, that laboratory and/or point-of-care measurement of residual platelet reactivity in a given individual while on treatment or following withdrawal can be useful to guide the timing of elective surgical intervention.

Clopidogrel

The well-described inter-individual 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 prior to elective cardiac surgery comes primarily from studies conducted between 2004 – 2019.

The 2009 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention recommended the withdrawal of clopidogrel for at least 5 days prior to CABG with only a level of evidence "C" (expert consensus opinion). However, a 2014 meta-analysis performed by Cao et al (of 5 studies from 2004 – 2009) compared the impact of fewer or more than five days of clopidogrel washout on perioperative bleeding, mortality, and morbidity in 2632 patients out of a larger cohort of 6385 for other analyses in the five studies (79). Patients

who had > 5 days of washout demonstrated a lower incidence of major bleeding (19.7% vs. 30.2%, P = 0.04), decreased need for reoperation (1.8% vs. 3.2%; P = 0.03) and a lower incidence of the composite endpoint that included mortality and myocardial infarction, recurrent ischemia, stroke, and emergency revascularization (7.9% vs. 9.7%, P= 0.01) by comparison to those with less than 5 days of washout. No statistical significance was demonstrated in the all-cause mortality rates between the 2 treatment groups (3.1% vs. 4.0%, P = 0.61).

More recently, in a 2016 retrospective analysis of prospectively collected data of 2,244 ACS DAPT patients who underwent either urgent or elective CABG, Hansson et al demonstrated that discontinuation of clopidogrel 3 – 5 days prior to surgery resulted in a higher rate of major bleeding complications compared to discontinuation greater than 5 days preoperatively (unadjusted OR 1.71 [95% CI 1.04 –2.79], P = 0.033) (70).

As well, Tomsic et al's 2016 retrospective observational cohort study of 626 patients on DAPT presenting for isolated on-pump CABG demonstrated that the subgroup of patients with clopidogrel withdrawn less than 5 days prior to elective cardiac surgery had higher transfusion needs (71.2 vs. 41.3%, P < 0.001), need for multiple transfusions (14.4 vs 3.7%, P < 0.001), and a higher incidence of mediastinal chest tube drainage ≥1000 ml in the first 12 hours postoperatively (26.4 vs 12.6%, P < 0.001) compared with those who remained only on aspirin (71). A trend was demonstrated toward the increased need for surgical re-exploration 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 = 0.051).

Ticagrelor

Ticagrelor is an oral direct-acting, competitive P2Y12 inhibitor, which, when compared to clopidogrel,

exhibits a faster onset and offset of effect, and more consistent inhibition of platelet function amongst individuals because it does not require metabolic activation (78,80).

Though it was appreciated that continuation of DAPT to the time of surgery would result in excessive bleeding (that 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 (64).

Given the known "fast offset" time of ticagrelor, subgroup analyses results from the 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 (68), 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's 2016 retrospective observational cohort study of 626 patients on DAPT presenting for isolated on-pump CABG demonstrated that the subgroup of patients with ticagrelor withdrawn less than 72 hours preoperatively had higher transfusion needs (72.1 vs 41.3%, $P < 0.001$), higher demand for multiple allogeneic blood transfusions (14.8 vs 3.7%, $P < 0.001$) and higher in-hospital mortality (4.9 vs 1.0%, $P = 0.019$) compared with those who remained only on aspirin, while those with ticagrelor withdrawn greater than 72 hours demonstrated no differences from the aspirin only group (71).

In the same 2016 analysis of 2,244 ACS DAPT patients who underwent either urgent or elective CABG described above for clopidogrel, Hansson et al demonstrated a significantly higher rate of major bleeding complications when ticagrelor was discontinued less than 3 days preoperatively compared with discontinuation at 3 – 5 days preoperatively [unadjusted OR 5.17 (95% CI 2.89 – 9.27), $P < 0.0001$] (70).

The authors also reported that mortality was significantly higher in patients with major bleeding complications [9.9 vs. 0.7%, unadjusted OR 14.78 (95% CI 7.82–27.93), P < 0.0001]. Preoperative thrombotic events were not reported, but postoperative thrombotic events prior to hospital discharge reportedly occurred in 2.3% of the ticagrelor group (compared to 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 demonstrated that ticagrelor exposure within 72 hours prior to cardiac surgery was associated with an increased risk of major bleeding complications (defined as the intraoperative transfusion of more than 1000 ml red blood cells, a postoperative bleeding volume greater than 2000 ml or the need for re-exploration for bleeding or cardiac tamponade) (81).

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 prior to elective cardiac surgical intervention is much less robust than for clopidogrel or ticagrelor.

The 2009 ACC/AHA guidelines recommended a prasugrel washout time of 7 days prior to elective cardiac surgical intervention to minimize bleeding, but this was based on expert consensus opinion (level of evidence C) (74).

Results from the 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 - >14 days prior to 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 > 5 days preoperatively, and only 29.1% of the prasugrel group for > 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 = 0.050), the incidence of platelet transfusion was significantly higher in the prasugrel group (17.96% vs. 9.82%; p = 0.033), and the mean number of platelet units transfused was also higher (0.78 U vs. 0.39 U; p = 0.047). No significant differences were found in red blood cell transfusion (2.1 U vs. 1.7 U; p = 0.442). A trend toward a higher incidence of surgical re-exploration for bleeding in the prasugrel group was detected (11 of 173 patients) compared to the clopidogrel group (4 of 173 patients), but a surgical source of bleeding was identified in 8 of the 11 prasugrel patients and in 3 of the 4 clopidogrel patients resulting in very small numbers of patients in whom the ongoing bleeding was likely due to coagulopathy (69).

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 prior to elective cardiac surgical intervention “should be considered” (82).

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 post-operative mediastinal re-exploration is the data provided by Ouattara et al (83). In this observational study of 217 consecutive ACS patients presenting for CABG with either 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 post-operative mediastinal re-exploration in the DAPT group compared to the SAPT group. The removal of aprotinin from the market in 2007 renders these results non-applicable to modern practice, and a subsequent prospective attempt to demonstrate a similar effect with tranexamic acid in 150 consecutive patients failed to do so (84).

Drugs Used for Intraoperative Blood Management

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

Lysine Analogues vs. Placebo

A large 2017 randomized trial of 4631 patients aimed to clarify the safety and efficacy profile of TXA. Patients were given 100 mg/kg TXA after induction, which was reduced to 50 mg/kg in January 2012 after 1392 pts were enrolled. TXA reduced both the need for RBCs ($p < 0.001$) and any blood product ($p < 0.001$) compared to placebo. The number needed to treat (NNT) for TXA to reduce transfusion of one unit of blood products was six. TXA also reduced the need for re-exploration (1.4% vs. 2.8%; RR: 0.49, 95% CI, 0.32 - 0.75; $p = 0.001$). There was no significant benefit for 30-day mortality or thromboembolic events. It should be noted that, although it was not a pre-selected outcome in our PICO question, this study raises questions on the association between TXA and seizures (85).

Other smaller RCTs such as that by Taghaddomi et al (86) and Esfandiari et al (87) confirmed the benefits of TXA over placebo in reducing bleeding and total transfusions, and the RCT by Taghaddomi et al and Wang et al (88) suggests that these benefits might extend to off-pump CABG patients as well, although over 10% of the randomized patients in Wang et al study 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 published a large RCT in 2011 of 1,550 patients taken from data published in the BART trial (89). There was no difference in any outcome between the two agents, except a reduction of FFP use in TXA (RR: 0.83, 98.33% CI, 0.72 - 0.96). The primary outcome of the study, as in the BART trial, was a composite outcome of bleeding from chest tubes that exceeded 1.5 liters during any 8-hour period or massive transfusion, which was defined as the administration of more than 10 units of red cells within 24 hours after surgery. In order 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 included three groups of 100 patients, each receiving either TXA, EACA, or placebo (90). EACA was superior to placebo and TXA at 6 hours, 12 hours, and 24 hours after surgery at 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, while 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 n=78 by Choudhuri et al compared EACA and TXA, and the only outcome of interest reported was a non-significant difference between the rate of re-exploration for bleeding amongst the three study groups (TXA n = 2, EACA n = 2, control n = 3; $p > 0.05$) (91). Due to the relative low quality of this study, the next best evidence is the retrospective cohort study by Keyl et al (92), which compared 341 patients in each group. TXA was superior at reducing blood loss (logistic regression OR: 0.57, 95% CI, 0.39 - 0.83; $p = 0.003$) and preventing the use of blood products (RBCs $p = 0.002$, FFP $p < 0.001$, platelets $p < 0.001$). This study also raises further questions on the association between TXA and seizures.

Martin et al also compared TXA vs. EACA in a 2011 retrospective cohort study of 604 patients (93). TXA significantly reduced 24-hour blood loss, but did not significantly reduce usage of any transfusion products, re-exploration, 30-day mortality, or thromboembolic events when compared to EACA.

A meta-analysis assessing the randomized and non-randomized 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, re-exploration due to bleeding, and thromboembolic events is not clearly established vs. control. The association between TXA and seizures is noted, and will be a point of emphasis for this guideline in the future.

Continuing Research on Aprotinin vs. Placebo and vs. Lysine Analogues

Despite the fact that aprotinin has been off the market in the United States and Europe since the BART study in 2008 due to safety concerns (94), our search identified five meta-analyses, two prospective randomized studies, and two retrospective observational studies published since the 2011 Blood Conservation Guidelines which continue to assess its safety and effectiveness either vs. other antifibrinolytic agents or 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. (95).

Two meta-analyses were published in 2009, both heavily influenced by the data from the BART study. Henry et al found no difference in rates of exploration, myocardial infarction, or 30-day mortality between aprotinin and either tranexamic acid (TXA) or epsilon aminocaproic acid (EACA), while aprotinin was more effective than EACA at preventing transfusion (96). McIlroy et al similarly found no increase in either mortality or thromboembolic events vs. placebo (97).

Complicating matters further, the meta-analyses by Ngaage and Bland and Hutton et al demonstrated a benefit in TXA vs. aprotinin in 30-day mortality, which held for RCT-only data and when combined with observational trials (95,98). However, the most recent network meta-analysis in 2013 by Howell et al similarly investigated the safety of aprotinin compared to TXA and EACA, and found no significant benefit for any agent in 30-day mortality, either compared to each other or placebo (99).

Two small prospective, randomized clinical trials and two retrospective studies were performed after these meta-analyses in 2012 didn't clarify the safety profile of aprotinin (100-103).

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

Intraoperative Non-Pharmacological 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 (104). Though 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 to 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, as blood transfusions can be both life-saving and deleterious to a patient depending on the context of the situation (105). In general, if improved or equivocal outcomes can be attained with a particular treatment relative to an alternative, and the need for transfusions is significantly less, such a therapy is looked upon favorably. For cardiac surgery, the above interplay is most relevant to decision-making with respect to thoracic aortic endografts, transcatheter valve technologies, minimally 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 (58) 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 (106). Further, although minimal access surgery is a heterogenous conglomerate of variable techniques, which impedes efforts for quality scientific assessment, best evidence would attribute a blood conservation advantage to these minimal access procedures (107,108)

Off-pump coronary surgery has consistently proven to reduce blood transfusions relative to on-pump coronary surgery (109,110). Yet, given variable results with respect to graft patency (110) and 5-year survival outcomes with off-pump procedures (111,112), routine use of this technique should be reserved for surgeons making a concerted commitment to integrate off-pump techniques into their daily operative practice.

Point of Care Hemostasis Testing

- **Goal directed transfusion algorithms which incorporate point of care testing, such as with viscoelastic devices, are recommended 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. Point-of-care monitoring of the hemostatic mechanism is critical in order 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 anti-thrombotic drugs. Viscoelastic tests are used for this purpose and constitute much of the data that has been published on POC testing of hemostasis in cardiac surgery, Point-of-care 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 (ACT) in certain instruments, however these measures are not recommended to supplant the traditional ACT measurements (113). Data supporting the use of viscoelastic testing will be presented without regard to the specific platform or instrument used and will be reported based upon the strength of the evidence. Point of care assessment of hemostasis is used to guide blood product administration and can reduce unnecessary transfusions by using a patient-directed approach to transfusion therapy. In reducing transfusions, viscoelastic testing has been shown to decrease costs by reducing transfusions (114,115) and the risks associated with transfusions (116,117).

Routine plasma-based coagulation testing results have a poor correlation and limited value in the perioperative management of patients with coagulopathic bleeding (118,119). These tests are performed on plasma and only represents the time to initiation of clot formation; they 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 two decades and has been incorporated into numerous patient blood management algorithms.

The use of POC-based transfusion algorithms using viscoelastic testing have resulted in significant reduction of allogeneic blood product transfusion in high-risk clinical settings such as cardiovascular surgery (120). A large prospective multicenter trial by Karkouti et al. included more than 7,000 cardiac surgery patients (121). The trial analyzed transfusion rates before and after implementation of a viscoelastic testing based transfusion algorithm plus a platelet function analyzer. The use of a POC-based transfusion algorithm resulted in a significant decrease in RBC and platelet transfusions. When used in conjunction with a specific POC platelet function analyzer, algorithms have demonstrated a significant blood-sparing effect when compared prospectively with standard laboratory testing.

Many studies that incorporate viscoelastic-based transfusion algorithms and demonstrate reduced transfusions substitute the early use of pro-hemostatic factor concentrates and fibrinogen concentrate for allogeneic blood (116). This practice reduces transfusions however, the use of PCCs and fibrinogen concentrate in place of blood products must be carefully evaluated for safety (122). This renders careful monitoring of hemostasis a critical part of this practice (123).

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 (124,125). It is questionable whether the individual investigations were powered to evaluate the impact of viscoelastic testing on morbidity and mortality. 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 (126,127), but these large scale studies have not yet been conducted.

Perfusion Interventions

ANH

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

Cardiopulmonary bypass (CPB) is responsible for multiple negative effects on circulating blood and blood components. Acute normovolemic hemodilution is a method to limit these effects on a portion of the patient's blood volume. Although there are no published standardized protocols for ANH, it typically involves the removal of 1 to 3 units of the patient's blood prior to heparinization. Currently ANH is an underutilized method in cardiac surgery. Goldberg et al, in an observational study showed that only 17% of patients had ANH performed prior to surgery (128). The reason for its underutilization may be due to the fact that it requires additional preoperative time, possible lack of attention to patient blood management strategies in general and real or perceived risks of ANH. Additionally, benefits of ANH are directly linked to the amount of whole blood that is withdrawn from the patient (128-130). 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 utilized for many decades, it is not until recently that randomized control trials and meta-analyses have been published. In a 2017 meta-analysis, Barile et al 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 -0.64 (95% CI, -0.97 to -0.31; $p < 0.001$) and a 26% reduced risk of transfusion (RR: 0.74, 95% CI, 0.62-0.87 $p < 0.001$; ARR: 14%) (131). Acute normovolemic hemodilution was also associated with 0.79 fewer units of RBCs used. The conclusions of this study are

limited by a very high degree of heterogeneity, which was due to differences in the amount of blood removed, the types of surgery, year of publication, and presence/absence of a transfusion protocol amongst the included studies. The size of the effect suggests to this group that there is likely a benefit to utilizing ANH, however the extent of that benefit is unclear.

When ANH is utilized with adequate volumes there is an apparent decrease in perioperative blood and blood product utilization. Consistently, the greater the amount of whole blood that can be removed from the patient without hemodynamic instability, the greater the effects of ANH (128). Care must be taken in patients that are preoperatively anemic, smaller patients that may have lower overall blood volumes and stable patients that 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 levels of hematocrits while on CPB, it may be useful to combine ANH with retrograde autologous priming (RAP). In the retrospective study of over 18,000 patients by Stammers et al, comparisons were made between patients that had RAP only, ANH only, RAP and ANH or neither (N). Lowest transfusion rates were seen in the ANH only cohort while the highest transfusion rates were seen in the (N) patients. (129). As a retrospective study, and as in many studies when it comes to blood conservation, it is difficult to draw firm conclusions due to patient acuity differences as well as physician and institutional commitment to a comprehensive multi-modality approach to patient blood management.

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 cardiopulmonary bypass (CPB) circuit should be utilized wherever possible. (Class I, Level B-R)**

Multiple small randomized prospective studies, and a moderate sized meta-analysis suggest that RAP is a simple, safe and effective process in order to decrease intra 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 of 557 patients in six trials concluded that patients in the RAP group had both fewer intraoperative transfusions (OR: 0.36, 95% CI, 0.13 - 0.94; p = 0.04) and fewer transfusions during their total stay (OR: 0.26, 95% CI, 0.13 - 0.52; p = 0.0001), with an NNT of 11 during the intraoperative period and 4 for the total stay. The study further reported a weighted mean difference of -0.60 units of RBCs used (95% CI, -0.90 to -0.31 units). Each of the 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 (132).

In a randomized, prospective study by Hofmann et al, intraoperative rates of transfusions were 17.2% in the non-RAP group versus only 3.7% in the RAP group, with an absolute risk reduction of 13.5 and an

NNT of 7.44 (133). No significant differences in amount of bleeding, mortality, re-exploration, or thromboembolic events were found. Likewise, a 2015 RCT by Cheng et al reported reductions in perioperative transfusion rates of 54.2% for RAP and 95.8% for non-RAP ($p < 0.01$). There were no significant differences in the amount of bleeding in this trial (134).

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 (Trendelenberg positioning) and/or pharmacological (vasoconstrictors) means. No recent studies show any increased risk from intra-operative RAP, and as such, the risk/benefit ratio is significantly in favor of RAP for patients at risk.

Minicircuits and Vacuum-Assisted Venous Drainage

- **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 2017, demonstrated in a registry study with over 47,000 patients, that the ratio of prime volume to estimated blood volume was an independent predictor of transfusion, with increased ratio (larger prime volumes) resulting in transfusion (135). Similarly Dickinson et al 2019 in a study evaluating over 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 (136). Each of these studies demonstrated associations of reduced hemodilution with decreased prime volume.

The adoption of a combined strategy of surgical approach, anesthesia, and perfusion management along with CPB circuit features designed to minimize hemodilution and optimize biocompatibility, has been termed minimally invasive extracorporeal circulation (MiECC). Configuration of the circuit components for MiECC have been defined by consensus to include a combination of multiple techniques (including a closed CPB circuit; biologically inert blood contact surfaces; reduced priming volume; a centrifugal pump; a membrane oxygenator; a heat exchanger; a cardioplegia system; a venous bubble trap/venous air removing device and a shed blood management system) (137).

Two meta-analyses in 2011 and 2013, supplemented by 3 additional RCT's, provide evidence for blood conservation benefits associated with MiECC. The meta-analyses compared MiECC and studies using conventional CPB in both CABG and valve surgeries in 29 and 24 studies respectively, with 18 studies in common (138,139). Both meta-analyses reported reduced RBC transfusion (OR 0.35 [95% CI, 0.23-0.53], I^2=0), (OR 0.24 [95% CI, 0.16-0.37], I^2=5%), and failed to show any difference in reoperation for bleeding. Blood loss in both studies was also reduced, albeit with substantial heterogeneity (WMD=−131.32 [95% Ci, −187.87 to −74.76], I^2=89%), (WMD=−137.93 [95% CI, −198.98 to −76.89], I^2=81%). Both meta-analyses reported no differences in 30d mortality, myocardial infarction, renal, and cerebral outcomes.

Three additional RCT's with sample sizes over 100 have been reported, which support the findings of the previously published meta-analyses. The trial by El-Essawi et al (2011) of 500 patients demonstrated decreased red blood cell transfusion requirement in MiECC group (199 ± 367 ml vs. 347 ± 594 ml, p <0.001), reoperation for bleeding 2.4 vs 6.1% (p<0.05), with transfusion as a whole (*35.3 vs 44.8%*), transfusion of packed RBC (28.6 vs 39.5%) and transfusion of FFP (17.5 vs 25.4%) all significantly lower in the MiECC patients (p=0.04, 0.01 and 0.04, respectively) (140). Anastasiadis et al (2013), in a RCT of 120

patients, reported intraoperative blood transfusion (units) 0.5 ± 0.7 versus 1.5 ± 1.1 p<0.001 and postoperative blood transfusion (units) 2 ± 1.7 vs. 3 ± 2.4; p = 0.009 to be lower in the MiECC group (141). Baumbach et al evaluated 200 MVR/AVR patients undergoing minimally invasive 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 = 0.003), whilst reporting no other clinical outcome differences apart from reduced delirium in the MiECC group (142).

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

Topical Hemostatic Agents

- **Antifibrinolytic agents applied into the surgical wound after CPB are reasonable interventions to limit chest tube drainage and transfusion requirements after cardiac operations using CPB. (Class IIA, Level B)**
- **Topical hemostatic agents that employ localized compression or provide wound sealing may be considered to provide local hemostasis at anastomotic sites as part of a multimodal blood management program. (Class IIB, Level C)**

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 (143) 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 controlled randomized trials is extremely difficult due to difficulty in establishing reliable endpoints and using reproducible bleeding scales intraoperatively may be the best method to compare efficacy of topical hemostatic agents.

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 over 8,000 patients have investigated the use of restrictive versus liberal RBC transfusion strategies in patients undergoing cardiac surgery (144-148). These studies have originated from 4 different countries and involved patients from all continents in the world. Although there were some differences in design, such as pre vs postoperative randomization and superiority vs non-inferiority comparisons, all included a restrictive trigger between 7 to 8 g/dL and a liberal trigger between 8 to 10 g/dL, and all had primary and

secondary outcomes that included important clinical events such as morbidity, mortality, and resource utilization including blood product exposure.

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

Another study randomized 722 adults in the US and India who were having valve or coronary artery bypass graft surgery to a restrictive (24% hematocrit) or liberal (28% hematocrit) transfusion threshold (146). The restrictive group received significantly fewer allogeneic transfusions (54% vs. 75%; $p < 0.001$). 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 over 5,000 adults having moderate to high-risk cardiac surgery with cardiopulmonary bypass to a restrictive transfusion strategy (hemoglobin transfusion threshold <7.5 g/dL), or a liberal one (threshold <9.5 g/dL in the OR and ICU;

<8.5 g/dL on the ward) (148). RBC transfusion occurred in 52.3% of the restrictive patients compared to 72.6% of the liberal group (OR: 0.41, 95% CI, 0.37 - 0.47; p < 0.001). Non-inferiority 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, re-hospitalization, or coronary revascularization (148).

In the Transfusion Indication Threshold Reduction (TITRe2) trial, 2007 patients who had undergone cardiac surgery with a post-operative hemoglobin level < 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 = 0.045]. 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 RBC transfusion (149-151). The probability of receiving allogeneic transfusion was significantly reduced by approximately 30% with restrictive transfusion (RR 0.69, 95% CI 0.67–0.71) and the transfusion risk was thus approximately 1.5 times higher in the liberal group. The average amount of transfusion was reduced by about 1 unit (WMD 0.87-0.90 units), and there was no significant difference in blood loss.

Although there were slight differences in the data analyses undertaken, all meta-analyses found no difference in mortality between transfusion strategies (odds ratios or risk ratios from 0.96 to 1.03) with low heterogeneity (I^2 0-21%). No significant subgroup interactions or heterogeneity were identified for type of surgery (elective vs non-elective), patient category (adult vs pediatric) or time of randomization (pre/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 terms of 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 reduce hemodilution and transfusion. (Class IIA, Level B-R)**
- **When using various crystalloid solutions relative to one another, there is no net benefit in patients who underwent cardiac surgery (Class III: No Benefit, Level C-LD)**

- **Hydroxyethyl starch is not recommended as a volume expander in cardiopulmonary bypass patients as it may increase the risk of bleeding. (Class III: No Benefit, Level B-R)**

Fluid boluses are common and responsible for a large proportion of the positive fluid balance seen in patients after cardiac surgery (153). The most common reason for fluid administration was hypotension (65%), and crystalloid fluid was used for 65% of the boluses (153). Crystalloid solutions that are commonly used in cardiac surgery, 0.9% (normal) saline, and buffered isotonic crystalloid solutions. There is evidence that the use of 0.9% saline (saline) may be associated with increased blood transfusion requirements compared with buffered crystalloids in non-surgical patient populations (154-157), as well as 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 on 100 adult cardiac surgery patients demonstrated that post-cardiac surgery fluid bolus therapy with 20% albumin when compared with crystalloid fluid resulted in less positive fluid balance as well as several hemodynamic and ICU treatment advantages (161). Another randomized prospective study of 240 elective cardiac surgery patients showed that despite equal blood loss from chest drains, albumin interfered with blood coagulation and produced greater hemodilution, which was associated with more transfusion of blood products compared with crystalloid use only (162). Two retrospective studies implementing albumin

reduction strategies found no difference in mortality and transfusion between crystalloid and albumin groups (163,164). Interestingly, a retrospective cohort study of 984 patients undergoing on-pump cardiac surgery showed a dose-dependent acute kidney injury risk associated with the administration of albumin (165). These retrospective studies carry significant limitations due to lack of vigorous variable control.

The extensive restriction of another commonly used colloid solution in cardiac surgery, hydroxyethyl starch (HES), was recommended by the European Medicines Agency in 2013 and mandated a change in volume management in cardiac surgery (166). A meta-analysis was performed of postoperative blood loss in randomized clinical trials of HES versus albumin for fluid management in adult cardiopulmonary bypass 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, with an interquartile range of 30 to 60. The indications for colloid use were volume expansion in 9 of the trials, pump priming in 5, and both in 4. Hydroxyethyl starch increased blood loss, reoperation for bleeding, and blood product transfusion after cardiopulmonary bypass. There was no evidence that these risks could be mitigated by lower molecular weight and substitution (167). In contrary, another meta-analysis of randomized clinical trials could not identify safety issues with tetrastarches compared with albumin or crystalloid solutions in terms of 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 9 were completely blinded. The duration of follow-up covered a wide range, from 2 hours to 30 days. The variations in inclusion of studies might explain the apparent differences in conclusions.

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

Two randomized controlled trials in the intensive care setting—the CHEST and 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 AKI 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).

Blood Salvage and Massive Transfusion

A recent study provided some helpful prediction algorithms and management options for patients at higher risk of massive transfusion (178). Risk factors for massive transfusion common to valve surgery alone, CABG alone, and their combination were identified. They include female sex, older age, renal

dysfunction, lower body mass index, lower preoperative hemoglobin, and longer CPB times. Several independent massive transfusion risks were identified specific to valve surgery and include: active endocarditis, non-atrial 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 having cardiac operations. One observational study evaluated the ideal ratio of FFP to RBC in patients having major cardiac operations requiring massive transfusion (179). These authors found that higher FFP/RBC ratios (sometimes approaching greater than 1:1 ratio) were associated with reduced risk of death, stroke, and myocardial infarction only in patients having cardiovascular operations and receiving massive transfusions (defined as more than 10 units of PRBCs in a single 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 following operations, as an extension from the trauma literature. This recommendation must be tempered with caution since even trauma surgeons have concerns about optimal transfusion therapy and evaluation of traumatic hemorrhage (180).

Intraoperative blood salvage using cell-saver 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).

Figure 1. Increased Association of Adverse Outcomes in Patients with Anemia and/or Transfusion from Ferraris, et al. Ann Surg (185)

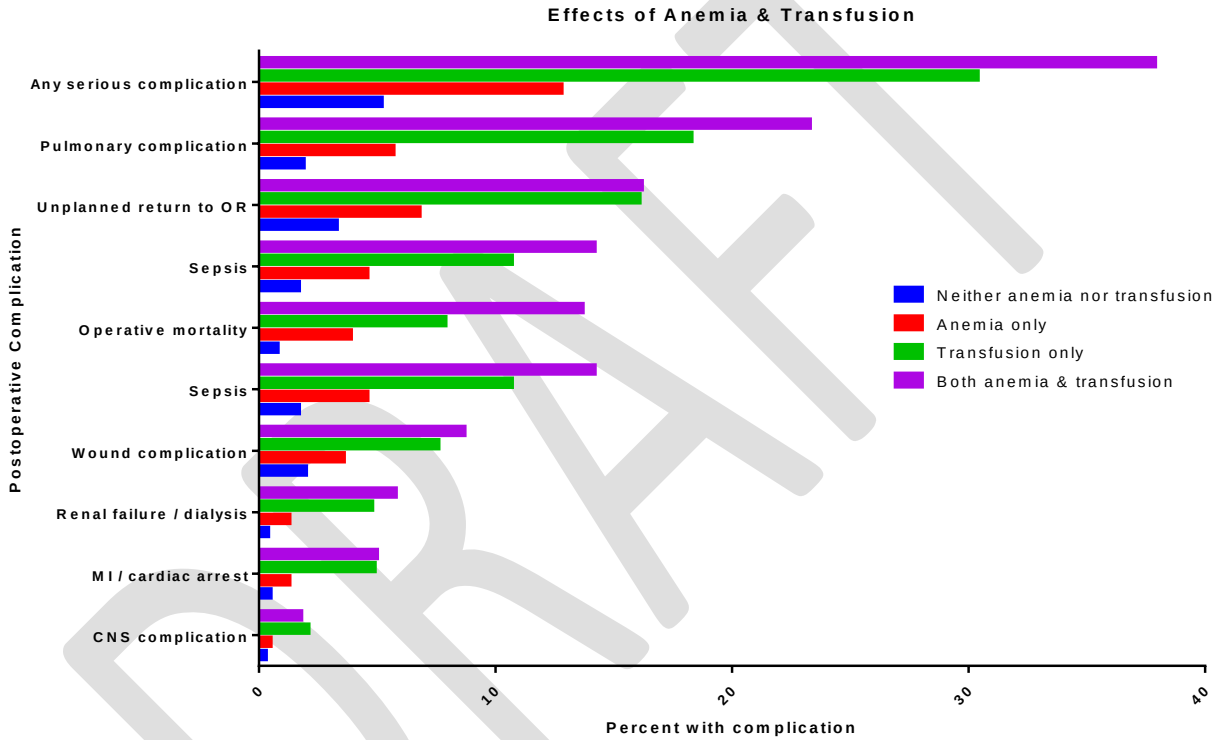

Table 2. All Current Recommendations for Patient Blood Management, Classified by Intervention Type and in Descending Order of Class of Recommendation and Level of Evidence

Intervention	ACC/AHA Class and Level
Preoperative Interventions	
Preoperative identification of high-risk patients should be performed, and all available preoperative and perioperative measures of blood conservation should be undertaken in this group as they account for the majority of blood products transfused.	**Class I, Level A**

Assessment of anemia and determination of its etiology is appropriate in all patients undergoing cardiac surgery and it is reasonable to treat with intravenous iron preparations if time permits.	**Class IIA, Level B-R**
In patients undergoing cardiac operations, it is reasonable to implement standardized transfusion protocols in order to reduce transfusion burden.	**Class IIA, Level B-R**
In patients who have (i) preoperative anemia, (ii) refuse blood transfusion, (iii) or are deemed high-risk for postoperative anemia, it is reasonable to administer preoperative erythropoietin stimulating agents and iron supplementation several days prior to cardiac operations to increase red cell mass.	**Class IIA Level B-R**
Minimization of phlebotomy by reduced volume and frequency of blood sampling is a reasonable means of blood conservation.	**Class IIA, Level B-NR**
Preoperative treatment of asymptomatic anemia and thrombocytopenia with transfusion is of uncertain benefit.	**Class III: No Benefit, Level B-NR**
Preoperative Antiplatelet Management	
In order to reduce bleeding in patients requiring elective cardiac surgery, ticagrelor should be withdrawn preoperatively for a minimum of 3 days, clopidogrel for 5 days and prasugrel for 7 days	**Class I, Level B-NR**
It is reasonable to discontinue low-intensity antiplatelet drugs (e.g., aspirin) only in purely elective patients without acute coronary syndromes before operation with the expectation that blood transfusion will be reduced.	**Class IIA, Level A**
Laboratory and/or point-of-care measurement of antiplatelet drug effect in patients having received recent dual antiplatelet therapy can be useful to assess bleeding risk or to guide timing of surgery.	**Class IIA, Level B-R**
The very early addition of a P2Y12 inhibitor to aspirin therapy in the postoperative care of coronary artery bypass grafting patients prior to ensuring surgical hemostasis may increase bleeding and the need for surgical re-exploration, and is not recommended.	**Class III: No Benefit, Level C-LD**
Preoperative Anticoagulants	

In patients in need of emergent cardiac surgery with recent ingestion of a non-vitamin 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 alfa for either apixaban or rivaroxaban at appropriate dose).	**Class IIA, Level C-LD**
If the antidote for the specified NOAC is not available, prothrombin concentrate is recommended, recognizing that the effective response may be variable.	**Class IIA, Level C-LD**
Pharmacological Agents	
Use of synthetic antifibrinolytic agents such as epsilon-aminocaproic acid (EACA) or tranexamic acid reduce blood loss and blood transfusion during cardiac procedures and are indicated for blood conservation (Class I, Level A).	**Class I, Level A**
Tranexamic acid 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's disease).	**Class IIB, Level B-NR**
Blood Products and Derivatives	
Antithrombin III concentrates are indicated to reduce plasma transfusion in patients with antithrombin mediated heparin resistance immediately before cardiopulmonary bypass.	**Class I, Level A**
When allogeneic blood transfusion is needed, it is reasonable to use leukoreduced donor blood, if available.	**Class IIA, Level B-R**
Plasma transfusion is reasonable in patients with serious bleeding in the context of multiple or single coagulation factor deficiencies when safer fractionated products are not available.	**Class IIA, Level B-NR**
Prothrombin concentrate is reasonable to consider over fresh frozen plasma as first line therapy for refractory coagulopathy in cardiac surgery in select situations to reduce bleeding.	**Class IIA, Level B-NR**

Use of recombinant factor VIIa concentrate may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB.	**Class IIB, Level B-NR**
Prophylactic use of plasma in cardiac operations in the absence of coagulopathy is not indicated, does not reduce blood loss and exposes patients to unnecessary risks and complications of allogeneic blood component transfusion.	**Class III: Harm, Level A**
Perfusion Interventions	
Retrograde autologous priming of the cardiopulmonary bypass (CPB) circuit should be utilized wherever possible.	**Class I, Level B-R**
Reduced priming volume in the CPB circuit reduces hemodilution and is indicated for blood conservation,	**Class I, Level B-NR**
Acute normovolemic hemodilution (ANH) is a reasonable method to reduce bleeding and transfusion.	**Class IIA, Level A**
Minimally Invasive extracorporeal circulation is reasonable to reduce blood loss and red cell transfusion as part of a combined blood conservation approach.	**Class IIA, Level B-R**
Use of modified ultrafiltration may be reasonable for blood conservation and reducing postoperative blood loss in adult cardiac operations using CPB.	**Class IIB, Level B-R**
Blood Salvage Interventions	
Routine use of red cell salvage using centrifugation is helpful for blood conservation in cardiac operations using CPB.	**Class I, Level A**
Centrifugation of pump-salvaged blood is reasonable for minimizing post-CPB allogeneic red blood cell transfusion.	**Class IIA, Level A**
In high-risk patients with known malignancy who require CPB, blood salvage using centrifugation of salvaged blood from the operative field may be considered when allogeneic transfusion is required.	**Class IIB, Level B-NR**
Direct reinfusion of shed mediastinal blood from postoperative chest tube drainage is not recommended as a means of blood conservation and may cause harm.	**Class III: Harm, Level B-NR**
Postoperative Fluid Management	

It is reasonable to administer human albumin after cardiac surgery to reduce hemodilution and transfusion.	**Class IIA, Level B-R**
Hydroxyethyl starch is not recommended as a volume expander in cardiopulmonary bypass patients as it may increase the risk of bleeding.	**Class III: No Benefit, B-R**
Use of various crystalloid solutions in relation to one another are not likely to affect blood loss or transfusion requirements	**Class III: No Benefit, Level C-LD**
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 point of care testing, such as with viscoelastic devices, are recommended to reduce periprocedural bleeding and transfusion in cardiac surgical patients.	**Class I, Level B-R**
Allogeneic RBC transfusion is unlikely to improve oxygen transport when the hemoglobin concentration is greater than 10 g/dL and is not recommended.	**Class III: No Benefit: Level B-R**
Management of Blood Resources	
A comprehensive multimodality blood conservation program led by a multidisciplinary team of health care providers should be part of any Patient Blood Management program to limit utilization of blood resources and decrease the risk of bleeding.	**Class I, Level B-R**

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, Cadellas M, Nunez-Matas MJ, Garcia-Erce JA. Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia 2017;72:826-834.

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? The Journal of thoracic and cardiovascular surgery 2016;152:1412-1420.
4. Hung M, Besser M, Sharples LD, Nair SK, Klein AA. 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, Halpin L, Ad N. 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, Neill SN, Vance JL, Likosky DS. The independent effects of anemia and transfusion on mortality after coronary artery bypass. The Annals of thoracic surgery 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. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2018;65:46-59.
8. Dai L, Mick SL, McCrae KR et al. Preoperative Anemia in Cardiac Operation: Does Hemoglobin Tell the Whole Story? The Annals of thoracic surgery 2018;105:100-107.
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. Transfusion medicine and hemotherapy : offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie 2018;45:42-46.
10. Padmanabhan H, Brookes MJ, Nevill AM, Luckraz H. Association Between Anemia and Blood Transfusion With Long-term Mortality After Cardiac Surgery. The Annals of thoracic surgery 2019;108:687-692.
11. 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. American Journal of Cardiology 2012;110:1021-1026.
12. 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. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2019;66:716-731.
13. 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. Anesthesia and analgesia 2019;128:981-992.
14. 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. American Journal of Nephrology 2009;30:253-260.
15. Tasanarong A, Duangchana S, Sumransurp S, Homvises B, Satdhabudha O. 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 Nephrology 2013;14:136.
16. Oh SW, Chin HJ, Chae DW, Na KY. Erythropoietin improves long-term outcomes in patients with acute kidney injury after coronary artery bypass grafting. J Korean Med Sci 2012;27:506-11.
17. Fisher JW. Pharmacologic modulation of erythropoietin production. Annual review of pharmacology and toxicology 1988;28:101-22.
18. 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.

19. Means RT, Jr. Clinical application of recombinant erythropoietin in the anemia of chronic disease. Hematology/oncology clinics of North America 1994;8:933-44.
20. 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;55:1644-1654.
21. 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. Journal of Thoracic & Cardiovascular Surgery 2010;139:621-626; discussion 626-627.
22. Penny-Dimri JC, Cochrane AD, Perry LA, Smith JA. Characterising the Role of Perioperative Erythropoietin for Preventing Acute Kidney Injury after Cardiac Surgery: Systematic Review and Meta-Analysis. Heart, Lung & Circulation 2016;25:1067-1076.
23. 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;393:2201-2212.
24. 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;49:1102-1108.
25. Ferraris V, Saha SP, Vyas KS, Rosengart TK. Blood Conservation – Balancing Risks and Benefits In: Frank SM, Waters JH, editors. Patient Blood Management: Multidisciplinary Approaches to Optimizing Care. Bethesda: AABB Press, 2016:345-370.
26. Padmanabhan H, Siau K, Curtis J et al. Preoperative Anemia and Outcomes in Cardiovascular Surgery: Systematic Review and Meta-Analysis. Ann Thorac Surg 2019;108:1840-1848.
27. 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;28:447-454.
28. Vlot EA, Verwijmeren L, van de Garde EMW, Kloppenburg GTL, van Dongen EPA, Noordzij PG. Intra-operative red blood cell transfusion and mortality after cardiac surgery. BMC Anesthesiol 2019;19:65.
29. Jabagi H, Boodhwani M, Tran DT, Sun L, Wells G, Rubens FD. The Effect of Preoperative Anemia on Patients Undergoing Cardiac Surgery: A Propensity-Matched Analysis. Semin Thorac Cardiovasc Surg 2019;31:157-163.
30. Yanagawa B, Rocha RV, Mazine A et al. Hemoglobin Optimization for Coronary Bypass: A 10-Year Canadian Multicenter Experience. Ann Thorac Surg 2019;107:711-717.
31. Ayoub K, Marji M, Ogunbayo G et al. Impact of Chronic Thrombocytopenia on In-Hospital Outcomes After Percutaneous Coronary Intervention. JACC Cardiovasc Interv 2018;11:1862-1868.
32. Sapiano MRP, Jones JM, Savinkina AA, Haass KA, Berger JJ, Basavaraju SV. Supplemental findings of the 2017 National Blood Collection and Utilization Survey. Transfusion 2020;60 Suppl 2:S17-s37.
33. Vassallo R, Goldman M, Germain M, Lozano M. Preoperative Autologous Blood Donation: Waning Indications in an Era of Improved Blood Safety. Transfus Med Rev 2015;29:268-75.
34. Martin K, Keller E, Gertler R, Tassani P, Wiesner G. Efficiency and safety of preoperative autologous blood donation in cardiac surgery: a matched-pair analysis in 432 patients. European Journal of Cardio-Thoracic Surgery 2010;37:1396-1401.
35. Lim MH, Je HG, Ju MH, Lee JH, Oh HR, Kim YR. Effects of Preoperative Autologous Blood Donation in Patients Undergoing Minimally Invasive Cardiac Surgery. Korean J Thorac Cardiovasc Surg 2019;52:385-391.

36. Zimmermann E, Zhu R, Ogami T et al. Intraoperative Autologous Blood Donation Leads to Fewer Transfusions in Cardiac Surgery. Ann Thorac Surg 2019;108:1738-1744.
37. Schloendorff v. Society of New York Hospital. New York Court of Appeals, 1914:92.
38. Cobbs v. Grant. 505: Supreme Court of California, 1972:229.
39. Perlin TM. Clinical Medical Ethics: Cases in Practice. Boston, MA: Little Brown & Co, 1992.
40. Ethics TACoSCo. Statement on recommendations for surgeons caring for patients who are Jehovah's Witnesses. American College of Surgeons, 2018.
41. Bodnaruk ZM, Wong Cj Fau - Thomas MJ, Thomas MJ. Meeting the clinical challenge of care for Jehovah's Witnesses.
42. Rogers DM, Crookston KP. The approach to the patient who refuses blood transfusion.
43. Informed Consent in Blood Transfusion and Cellular Therapies: Patients, Donors, and Research Subjects. Bethesda, MD: AABB Press, 2007.
44. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National Trends in Ambulatory Oral Anticoagulant Use. The American journal of medicine 2015;128:1300-5.e2.
45. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and Variation in Oral Anticoagulant Choice in Patients with Atrial Fibrillation, 2010-2017. Pharmacotherapy 2018;38:907-920.
46. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine 2009;361:1139-51.
47. Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine 2011;365:883-91.
48. Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine 2011;365:981-92.
49. Giugliano RP, Ruff CT, Braunwald E et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine 2013;369:2093-104.
50. Douxfils J, Ageno W, Samama CM et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. Journal of thrombosis and haemostasis : JTH 2018;16:209-219.
51. 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-e633.
52. 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;118:437-450.
53. 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;73:1535-1545.
54. 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.
55. Hassan K, Bayer N, Schlingloff F et al. Bleeding Complications After Use of Novel Oral Anticoagulants in Patients Undergoing Cardiac Surgery. Annals of Thoracic Surgery 2018;105:702-708.
56. 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;34:419-423.
57. 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.
58. 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. The Annals of thoracic surgery 2011;91:944-82.

59. 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.
60. Cappabianca G, Mariscalco G, Biancari F et al. Safety and efficacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery. Critical Care (London, England) 2016;20:5.
61. Roman M, Biancari F, Ahmed AB et al. Prothrombin Complex Concentrate in Cardiac Surgery: A Systematic Review and Meta-Analysis. The Annals of thoracic surgery 2019;107:1275-1283.
62. 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.
63. 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.
64. 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.
65. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. The New England journal of medicine 2001;345:494-502.
66. Steinhubl SR, Berger PB, Mann JT, 3rd et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. Jama 2002;288:2411-20.
67. 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.
68. 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.
69. 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.
70. 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. European Heart Journal 2016;37:189-197.
71. Tomsic A, Schotborgh MA, Manshanden JS, Li WW, de Mol BA. Coronary artery bypass grafting-related bleeding complications in patients treated with dual antiplatelet treatment. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2016;50:849-856.
72. Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. Pharmacotherapy 2008;28:376-92.

73. 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.
74. 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.
75. 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). European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2014;46:517-92.
76. 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.
77. 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.
78. 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.
79. 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. Journal of Thoracic & Cardiovascular Surgery 2014;148:3092-3098.
80. 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.
81. Kremke M, Gissel MS, Jensen MJ, Thomassen SA, Jakobsen CJ. The association between a three-day ticagrelor discontinuation and perioperative bleeding complications. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2019;55:714-720.
82. 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. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2018;53:34-78.
83. 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.
84. 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. British Journal of Anaesthesia 2016;117:749-757.
85. Myles PS, Smith JA, Forbes A et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. New England Journal of Medicine 2017;376:136-148.
86. Taghaddomi RJ, Mirzaee A, Attar AS, Shirdel A. Tranexamic acid reduces blood loss in off-pump coronary artery bypass surgery. Journal of Cardiothoracic & Vascular Anesthesia 2009;23:312-315.

87. Esfandiari BR, Bistgani MM, Kabiri M. Low dose tranexamic acid effect on post-coronary artery bypass grafting bleeding. Asian Cardiovascular & Thoracic Annals 2013;21:669-674.
88. 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. Anesthesia & Analgesia 2012;115:239-243.
89. Raghunathan K, Connelly NR, Kanter GJ. epsilon-Aminocaproic acid and clinical value in cardiac anesthesia. Journal of Cardiothoracic & Vascular Anesthesia 2011;25:16-19.
90. 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. Journal of Cardiovascular and Thoracic Research 2014;6:197-202.
91. 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. Ethiopian Journal of Health Sciences 2015;25:273-278.
92. Keyl C, Uhl R, Beyersdorf F et al. High-dose tranexamic acid is related to increased risk of generalized seizures after aortic valve replacement. European Journal of Cardio-Thoracic Surgery 2011;39:e114-121.
93. Martin K, Knorr J, Breuer T et al. Seizures after open heart surgery: comparison of epsilon-aminocaproic acid and tranexamic acid. Journal of Cardiothoracic & Vascular Anesthesia 2011;25:20-25.
94. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery (New England Journal of Medicine (2008) 358, (2319-2331)). New England Journal of Medicine 2010;363:1290.
95. Hutton B, Joseph L, Fergusson D, Mazer CD, Shapiro S, Tinmouth A. Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies. Bmj 2012;345:e5798.
96. Henry D, Carless P, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ Canadian Medical Association Journal 2009;180:183-193.
97. McIlroy DR, Myles PS, Phillips LE, Smith JA. Antifibrinolytics in cardiac surgical patients receiving aspirin: a systematic review and meta-analysis. British Journal of Anaesthesia 2009;102:168-178.
98. 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. European Journal of Cardio-Thoracic Surgery 2010;37:1375-1383.
99. Howell N, Senanayake E, Freemantle N, Pagano D. Putting the record straight on aprotinin as safe and effective: results from a mixed treatment meta-analysis of trials of aprotinin. Journal of Thoracic & Cardiovascular Surgery 2013;145:234-240.
100. Mansouri M, Attary M, Bagheri K, Massoumi G, Ghavami B. Comparative evaluation of the effects of tranexamic acid and low-dose aprotinin on post-valvular heart surgery bleeding and allogenic transfusion. Interactive Cardiovascular & Thoracic Surgery 2012;15:23-27.
101. Nejad MHG, Baharestani B, Esfandiari R, Hashemi J, Panahipoor A. Evaluation and comparison of using low-dose aprotinin and tranexamic acid in CABG: A double blind randomized clinical trial. Journal of Tehran University Heart Center 2012;7:15-18.
102. Riddell RE, Buth KJ, Sullivan JA. The risks associated with aprotinin use: a retrospective study of cardiac cases in Nova Scotia. Canadian Journal of Anaesthesia 2013;60:16-23.
103. Deloge E, Amour J, Provenchère S, Rozec B, Scherrer B, Ouattara A. Aprotinin vs. Tranexamic acid in isolated coronary artery bypass surgery: A multicentre observational study. European Journal of Anaesthesiology 2017;34:280-287.

104. Myles PS. Meaningful outcome measures in cardiac surgery. The journal of extra-corporeal technology 2014;46:23-7.
105. Ferraris VA, Hochstetler M, Martin JT, Mahan A, Saha SP. Blood transfusion and adverse surgical outcomes: The good and the bad. Surgery 2015;158:608-17.
106. 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.
107. Kirmani BH, Jones SG, Malaisrie SC, Chung DA, Williams RJ. Limited versus full sternotomy for aortic valve replacement. The Cochrane database of systematic reviews 2017;4:Cd011793.
108. Sundermann SH, Sromicki J, Rodriguez Cetina Biefer H et al. Mitral valve surgery: right lateral minithoracotomy or sternotomy? A systematic review and meta-analysis. The Journal of thoracic and cardiovascular surgery 2014;148:1989-1995.e4.
109. Shroyer AL, Grover FL, Hattler B et al. On-pump versus off-pump coronary-artery bypass surgery. The New England journal of medicine 2009;361:1827-37.
110. Lamy A, Devereaux PJ, Prabhakaran D et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. The New England journal of medicine 2012;366:1489-97.
111. Lamy A, Devereaux PJ, Prabhakaran D et al. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. The New England journal of medicine 2016;375:2359-2368.
112. Shroyer AL, Hattler B, Grover FL. Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass. The New England journal of medicine 2017;377:1898-1899.
113. 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. The Annals of thoracic surgery 2018;105:650-662.
114. Ak K, Isbir CS, Tetik S et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. Journal of Cardiac Surgery 2009;24:404-410.
115. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesthesia and analgesia 1999;88:312-9.
116. 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.
117. 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. The Journal of surgical research 2016;203:424-33.
118. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schochl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? Br J Anaesth 2015;114:217-24.
119. Toulon P, Ozier Y, Ankri A, Fleron MH, Leroux G, Samama CM. Point-of-care versus central laboratory coagulation testing during haemorrhagic surgery. A multicenter study. Thromb Haemost 2009;101:394-401.
120. 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.
121. 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;134:1152-1162.

122. Afshari A, Wikkelso A, Brok J, Moller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. The Cochrane database of systematic reviews 2011:Cd007871.
123. Dirkmann D, Gorlinger K, Dusse F, Kottenberg E, Peters J. 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.
124. Corredor C, Wasowicz M, Karkouti K, Sharma V. 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.
125. Lodewyks C, Heinrichs J, Grocott HP et al. Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: a systematic review and meta-analysis. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2018;65:1333-1347.
126. Groves DS, Winegar DA, Fernandez LG, Huffmyer JL, Viola F. Comparison of Coagulation Parameters in Arterial and Venous Blood in Cardiac Surgery Measured Using the Quantra System. J Cardiothorac Vasc Anesth 2019;33:976-984.
127. 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;75:366-373.
128. Goldberg J, Paugh TA, Dickinson TA et al. Greater Volume of Acute Normovolemic Hemodilution May Aid in Reducing Blood Transfusions After Cardiac Surgery. Annals of Thoracic Surgery 2015;100:1581-1587; discussion 1587.
129. Stammers AH, Mongero LB, Tesdahl E, Stasko A, Weinstein S. The effectiveness of acute normolvolemic hemodilution and autologous prime on intraoperative blood management during cardiac surgery. Perfusion 2017;32:454-465.
130. 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 Anesthesiology 2017;17:13.
131. 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. Anesthesia and analgesia 2017;124:743-752.
132. Saczkowski R, Bernier PL, Tchervenkov CI, Arellano R. Retrograde autologous priming and allogeneic blood transfusions: a meta-analysis. Interactive cardiovascular and thoracic surgery 2009;8:373-6.
133. 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.
134. Cheng M, Li JQ, Wu TC, Tian WC. Short-Term Effects and Safety Analysis of Retrograde Autologous Blood Priming for Cardiopulmonary Bypass in Patients with Cardiac Valve Replacement Surgery. Cell biochemistry and biophysics 2015;73:441-446.
135. Sun BC, Dickinson TA, Tesdahl EA, Likosky DS, Wells C, Weinstein S. The Unintended Consequences of Over-Reducing Cardiopulmonary Bypass Circuit Prime Volume. Annals of Thoracic Surgery 2017;103:1842-1848.
136. Dickinson TA, Wu X, Sturmer DL et al. Net Prime Volume Is Associated with Increased Odds of Blood Transfusion. The journal of extra-corporeal technology 2019;51:195-200.
137. 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). Interactive cardiovascular and thoracic surgery 2016;22:647-62.

138. 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 journal (American Society for Artificial Internal Organs : 1992) 2011;57:141-51.
139. Anastasiadis K, Antonitsis P, Haidich AB, Argiriadou H, Deliopoulos A, Papakonstantinou C. 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.
140. 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.
141. 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.
142. Baumbach H, Rustenbach CJ, Ahad S et al. Minimally Invasive Extracorporeal Bypass in Minimally Invasive Heart Valve Operations: A Prospective Randomized Trial. The Annals of thoracic surgery 2016;102:93-100.
143. 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;161:771-781.
144. Hajjar LA, Vincent JL, Galas FR et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. Jama 2010;304:1559-1567.
145. Murphy GJ, Pike K, Rogers CA et al. Liberal or restrictive transfusion after cardiac surgery. Erratum appears in N Engl J Med. 2015 Jun 4;372(23):2274; PMID: 26039619. New England Journal of Medicine 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. Annals of Thoracic Surgery 2017;104:1243-1250.
147. Shehata N, Burns LA, Nathan H et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion 2012;52:91-99.
148. Mazer CD, Whitlock RP, Fergusson DA et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. New England Journal of Medicine 2017;377:2133-2144.
149. Mueller MM, Van Remoortel H, Meybohm P et al. Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference. Jama 2019;321:983-997.
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;47:179-185.
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;40:1081-1088.
152. Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. 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, McCarthy LW. Intravenous fluid use after cardiac surgery: a multicentre, prospective, observational study. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine 2014;16:164-9.
154. Brummel-Ziedins K, Whelihan MF, Ziedins EG, Mann KG. The resuscitative fluid you choose may potentiate bleeding. The Journal of 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. The Journal of trauma 2006;61:57-64; discussion 64-5.

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. Annals of surgery 2012;255:821-9.
157. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesthesia and analgesia 2001;93:817-22.
158. Zhou F, Cove ME, Peng ZY, Bishop J, Singbartl K, Kellum JA. Normal saline resuscitation worsens lactic acidosis in experimental sepsis. Critical 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;31:1630-1638.
160. Human albumin solution for resuscitation and volume expansion in critically ill patients. The Cochrane database of systematic reviews 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;33:2920-2927.
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. British Journal of Anaesthesia 2014;112:255-264.
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;38:1241-1249.
164. Rabin J, Meyenburg T, Lowery AV, Rouse M, Gammie JS, Herr D. Restricted Albumin Utilization Is Safe and Cost Effective in a Cardiac Surgery Intensive Care Unit. The Annals of thoracic surgery 2017;104:42-48.
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. Agency EM. Hydroxyethyl-starch solutions (HES) no longer to be used in patients with sepsis or burn injuries or in critically ill patients. EMA, 2018.
167. Navickis RJ, Haynes GR, Wilkes MM. Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials. The Journal of thoracic and cardiovascular surgery 2012;144:223-30.
168. Jacob M, Fellahi JL, Chappell D, Kurz A. The impact of hydroxyethyl starches in cardiac surgery: a meta-analysis. Crit Care 2014;18:656.
169. Magder S, Potter BJ, Varennes BD, Doucette S, Fergusson D. 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, Raivio P, Kukkonen S, Niemi T. 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. The New England journal of medicine 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. The New England journal of medicine 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;117:458-463.

175. Alavi SM, Ahmadi BB, Baharestani B, Babaei T. 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, Liebold A, Gorki H. 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;32:205-211.
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 (Baltimore) 2019;98:e14219.
179. Tsukinaga A, Maeda T, Takaki S, Michihata N, Ohnishi Y, Goto T. Relationship between fresh frozen plasma to packed red blood cell transfusion ratio and mortality in cardiovascular surgery. Journal of anesthesia 2018;32:539-546.
180. Tran A, Matar M, Lampron J, Steyerberg E, Taljaard M, Vaillancourt C. Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: A systematic review and meta-analysis. The journal of trauma and acute care surgery 2018;84:505-516.
181. Sikorski RA, Rizkalla NA, Yang WW, Frank SM. 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.
185. Ferraris VA, Ferraris SP, Joseph O, Wehner P, Mentzer RM. Aspirin and postoperative bleeding after coronary artery bypass grafting. Annals of Surgery 2002;235:820-826.