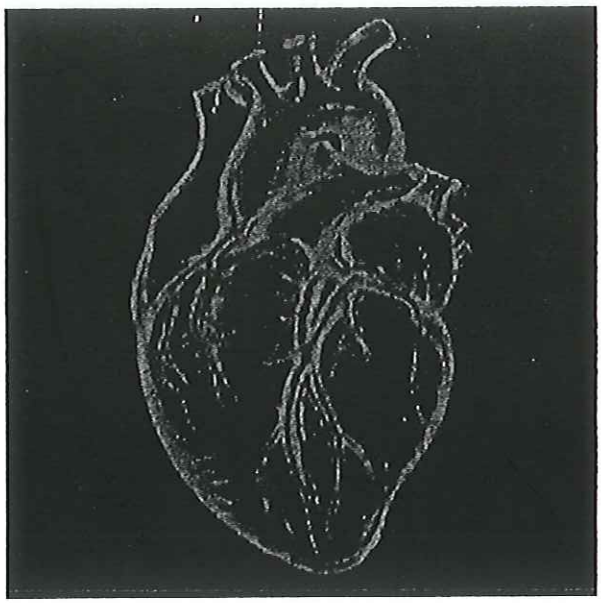
Strategies To Reduce Transfusions In Cardiac Surgery



Strategies to Reduce Transfusions in Cardiac Surgery

1) Preoperative Considerations

- Identify the patients at high risk of requiring transfusions.
- Consider preoperative Human Recombinant Erythropoietin.
- Attention to careful fluid management upon admission to the hospital.

2) Perioperative Techniques

- *Anesthesia Techniques*
  - Careful attention to fluid management pre-bypass.
  - Administration of Amicar or Tranexamic Acid.
  - Consider DDAVP post-bypass for those patients with pre-operative antiplatelet therapy and/or extended bypass times.
  - Consider a PCC (Kcentra) for intractable bleeding after FFP and PLT have been given.
  - Use of topical antifibrinolytics (Amicar) post-bypass for bleeding.

- *Perfusion Techniques*
  - Miniaturize the circuit.
  - Use appropriate size oxygenator.
  - Use retrograde autologous priming (RAP).
  - Use Acute Normovolemic Hemodilution (ANH) on select patients.
  - Use the ZBUF technique after removal of the cross clamp.

3) Multidisciplinary Approach

- Give thought to a transfusion algorithm which everyone agrees on.
- Change of mindset regarding transfusions. Consider the whole patient's physiological condition before a transfusion – inadequate oxygenation?

Najafi M *et al.* Hemoglobin optimization in cardiac surgery

Guidelines	Release date	Hemoglobin threshold definition	Level of evidence
Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists[33]	2011	6 g/dL preoperative and on CPB	2C
		7 g/dL postoperative and at risk of ischemia on CPB	2C
British Committee for Standards in Haematology[34]	2012	7 g/dL stable, non-bleeding CAD	C
		8-9 g/dL ACS	
The American Association of Blood Banks[35]	2012	7-8 g/dL in stable patients	1A
		8 g/dL in patients with CVD	2B
		No number for ACS	Uncertain recommendation; very low-quality evidence
European Society of Anesthesiology[36]	2013	7-9 g/dL in bleeding patients	1C
American Society of Anesthesiologists[37]	2015	No number	-

1A: Strong recommendation, high-quality evidence; 1B: Strong recommendation, moderate-quality evidence; 1C: Strong recommendation, low-quality

Cost of Blood Products

1. PRBC - Cost to hospital $200 plus type and crossmatch $396.
   Billed to patient $503.

2. FFP - Cost to hospital $60.
   Billed to patient $215.

3. Platelets - Cost to hospital $700.
   Billed to patient $1,791.

Review of Drugs to Reduce Transfusions in Cardiac Surgery

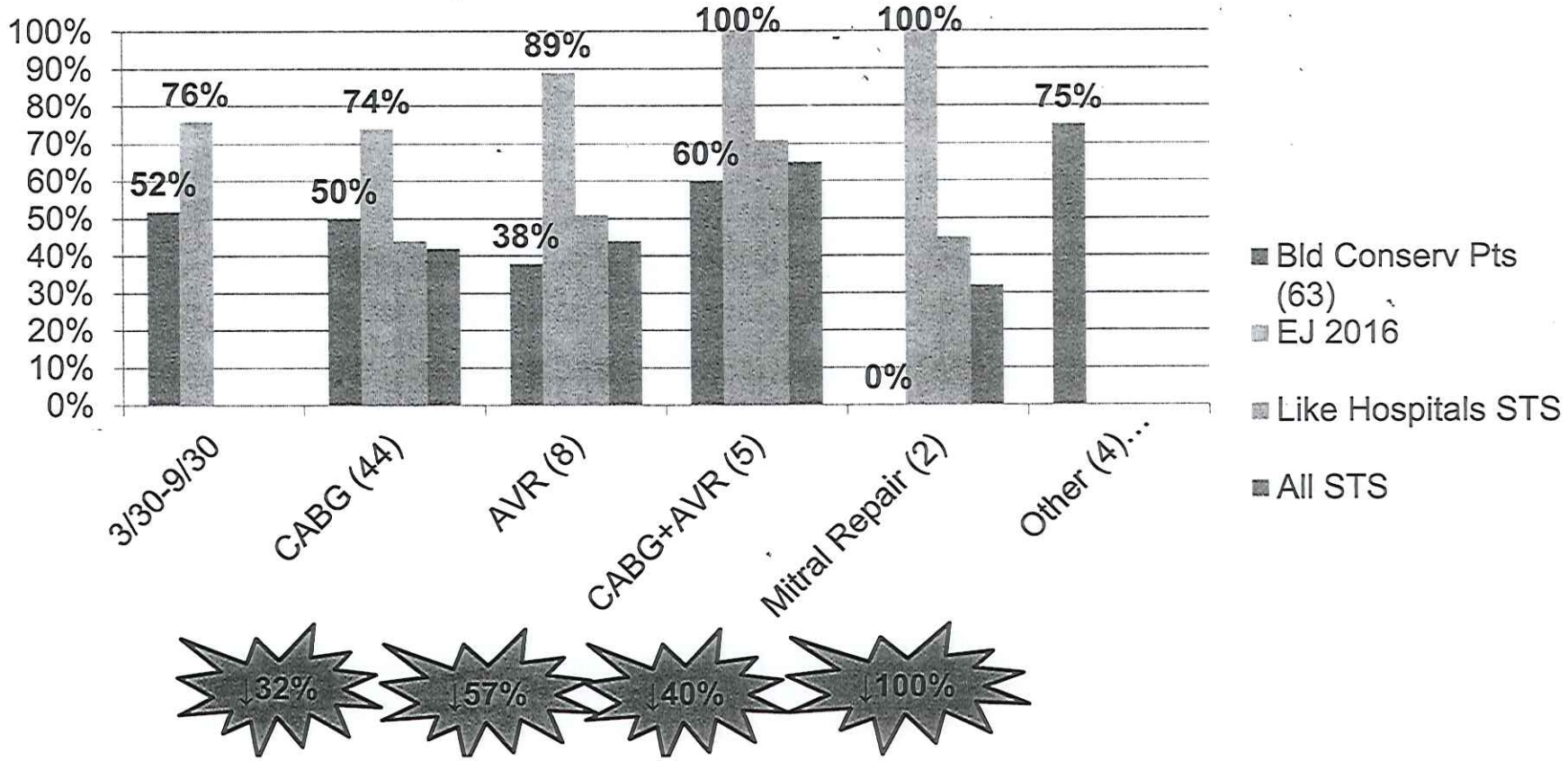
1. **Amicar and Tranexamic Acid – Antifibrinolytics**
    - Lysine analogs.
    - Stimulate the release of the amino acid Lysine which binds to plasminogen not allowing it to be transformed into plasmin.
    - Plasmin is what binds to fibrin causing its breakdown (fibrinolysis).
    - Can be used in conjunction with PCC's/DDAVP.
    - Amicar 5Gm is $5.39 and TXA 100mg is $13.73.

2. **DDAVP (Desmopressin)**
    - Used to treat some forms of diabetes.
    - Also used as an antidieuretic.
    - Stimulates the release of von Willebrand Factor and Factor VIII.
    - Improves platelet function.
    - Usually administered when patient is on preop antiplatelet therapy or in danger of having postop platelet dysfunction (CPB greater than 120 – 140 min).
    - Dose is 0.3mcg/kg.
    - Cost $285.

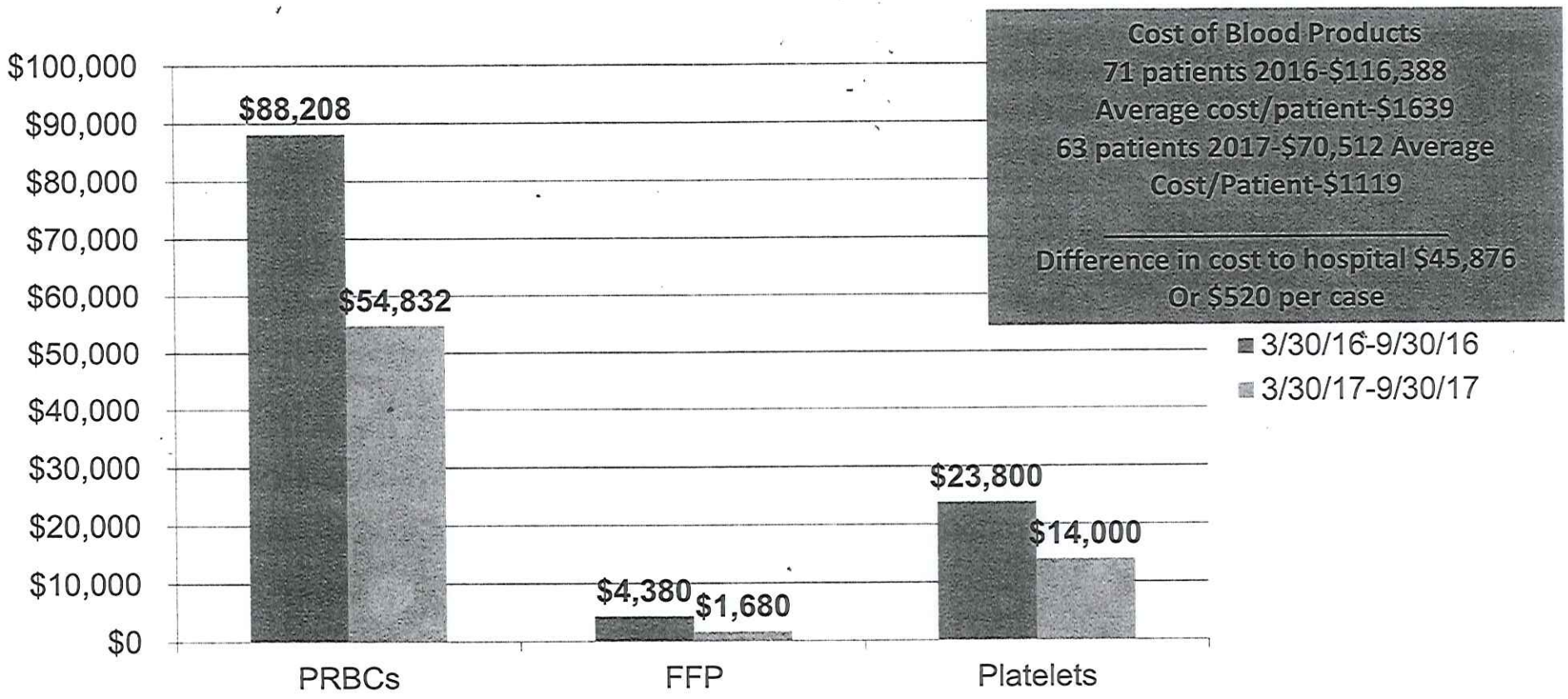
3. **Prothrombin Complex Concentrates (PCC)**
    - Pharmacy offers KCentra (Beriplex) – 4 factor PCC
    - Contain Factors II, VII, IX, and X.
    - Usually administered as a rescue treatment (with Antifibrinolytic and DDAVP).
    - Dosing usually 15-25 U/kg.
    - Cost of KCentra $670/500unit vial.
    - It is a human blood product

Use of Blood Products in 63 Patients During Blood Conservation Project

(No benchmark available for all surgeries)



Cost of Blood Products in Cardiac Surgery



2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines*

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SPECIAL REPORT

Background. Practice guidelines reflect published literature. Because of the ever changing literature base, it is necessary to update and revise guideline recommendations from time to time. The Society of Thoracic Surgeons recommends review and possible update of previously published guidelines at least every three years. This summary is an update of the blood conservation guideline published in 2007.

Methods. The search methods used in the current version differ compared to the previously published guideline. Literature searches were conducted using standardized MeSH terms from the National Library of Medicine PUBMED database list of search terms. The following terms comprised the standard baseline search terms for all topics and were connected with the logical 'OR' connector—Extracorporeal circulation (MeSH number E04.292), cardiovascular surgical procedures (MeSH number E04.100), and vascular diseases (MeSH number C14.907). Use of these broad search terms allowed specific topics to be added to the search with the logical 'AND' connector.

Results. In this 2011 guideline update, areas of major revision include: 1) management of dual anti-platelet therapy before operation, 2) use of drugs that augment red blood cell volume or limit blood loss, 3) use of blood derivatives including fresh frozen plasma, Factor XIII, leukoreduced red blood cells, platelet plasmapheresis,

*The International Consortium for Evidence Based Perfusion formally endorses these guidelines.

The Society of Thoracic Surgeons Clinical Practice Guidelines are intended to assist physicians and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. Moreover, these guidelines are subject to change over time, without notice. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

For the full text of this and other STS Practice Guidelines, visit http://www.sts.org/resources-publications at the official STS Web site (www.sts.org).

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See Appendix 2 for financial relationship disclosures of authors.

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recombinant Factor VII, antithrombin III, and Factor IX concentrates, 4) changes in management of blood salvage, 5) use of minimally invasive procedures to limit perioperative bleeding and blood transfusion, 6) recommendations for blood conservation related to extracorporeal membrane oxygenation and cardiopulmonary perfusion, 7) use of topical hemostatic agents, and 8) new insights into the value of team interventions in blood management.

Conclusions. Much has changed since the previously published 2007 STS blood management guidelines and this document contains new and revised recommendations.

(Ann Thorac Surg 2011;91:944–82)

1) Executive Summary

Introduction—Statement of the Problem

In the United States, surgical procedures account for transfusion of almost 15 million units of packed red blood cells (PRBC) every year. Despite intense interest in blood conservation and minimizing blood transfusion, the number of yearly transfusions is increasing [1]. At the same time, the blood donor pool is stable or slightly decreased [1, 2]. Donor blood is viewed as a scarce resource that is associated with increased cost of health care and significant risk to patients (http://www.hhs.gov/ophs/bloodsafety/2007nbcus_survey.pdf).

Perioperative bleeding requiring blood transfusion is common during cardiac operations, especially those procedures that require cardiopulmonary bypass (CPB). Cardiac operations consume as much as 10% to 15% of the nation's blood supply, and evidence suggests that this fraction is increasing, largely because of increasing complexity of cardiac surgical procedures. The majority of patients who have cardiac procedures using CPB have sufficient wound clotting after reversal of heparin and do not require transfusion. Nevertheless, CPB increases the need for blood transfusion compared with cardiac procedures done "off-pump" (OPCABG) [3]. Real-world experience based on a large sample of patients entered into The Society of Thoracic Surgeons Adult Cardiac Surgery Database suggests that 50% of patients undergoing cardiac procedures receive blood transfusion [4]. Complex cardiac operations like redo procedures, aortic operations, and implantation of ventricular assist devices require blood transfusion with much greater frequency [4–6]. Increasing evidence suggests that blood transfusion during cardiac procedures portends worse short- and long-term outcomes [7, 8]. Interventions aimed at reducing bleeding and blood transfusion during cardiac procedures are an increasingly important part of quality improvement and are likely to provide benefit to the increasingly complex cohort of patients undergoing these operations.

The Society of Thoracic Surgeons Workforce on Evidence Based Surgery provides recommendations for practicing thoracic surgeons based on available medical evidence. Part of the responsibility of the Workforce on Evidence Based Surgery is to continually monitor published literature and to periodically update recommendations when new information becomes available. This document represents the first revision of a guideline by the Workforce and deals with recent new information on blood conservation associated with cardiac operations. This revision contains new evidence that alters or adds to the 61 previous recommendations that appeared in the 2007 Guideline [9].

Abbreviations and Acronyms

ACS	= acute coronary syndrome
AT	= antithrombin
CABG	= coronary artery bypass graft surgery
CI	= confidence interval
CPB	= cardiopulmonary bypass
ECC	= extracorporeal circuit
ECMO	= extracorporeal membrane oxygenation
EPO	= erythropoietin
FDA	= Food and Drug Administration
FFP	= fresh-frozen plasma
ICU	= intensive care unit
MUF	= modified ultrafiltration
OPCABG	= off-pump coronary artery bypass graft surgery
PCC	= prothrombin complex concentrate
PRBC	= packed red blood cells
PRP	= platelet-rich plasma
r-FVIIa	= recombinant activated factor VII
RR	= relative risk
TEVAR	= thoracic endovascular aortic repair
VAVD	= vacuum-assisted venous drainage
ZBUF	= zero-balanced ultrafiltration

2) Methods Used to Survey Published Literature

The search methods used to survey the published literature changed in the current version compared with the previously published guideline. In the interest of transparency, literature searches were conducted using standardized MeSH terms from the National Library of Medicine PUBMED database list of search terms. The following terms comprised the standard baseline search terms for all topics and were connected with the logical "OR" connector: extracorporeal circulation (MeSH number E04.292 includes extracorporeal membrane oxygenation [ECMO], left heart bypass, hemofiltration, hemoperfusion, and cardiopulmonary bypass), cardiovascular surgical procedures (MeSH number E04.100 includes OPCABG, CABG, myocardial revascularization, all valve operations, and all other operations on the heart), and vascular diseases (MeSH number C14.907 includes dissections, aneurysms of all types including left ventricular aneurysms, and all vascular diseases). Use of

SPECIAL REPORT

these broad search terms allowed specific topics to be added to the search with the logical "AND" connector. This search methodology provided a broad list of generated references specific for the search topic. Only English language articles contributed to the final recommendations. For almost all topics reviewed, only evidence relating to adult patients entered into the final recommendations, primarily because of limited availability of high-quality evidence relating to pediatric patients having cardiac procedures. Members of the writing group, assigned to a specific topic, made recommendations about blood conservation and blood transfusion associated with cardiac operations based on review of important articles obtained using this search technique. The quality of information on a given blood conservation topic allowed assessment of the level of evidence as recommended by the AHA/ACCF Task Force on Practice Guidelines (http://www.americanheart.org/downloadable/heart/1260477059730120 9Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf).

Writers assigned to the various blood conservation topics wrote and developed new or amended recommendations, but each final recommendation that appears in this revision was approved by at least a two-thirds majority favorable vote from all members of the writing group. Appendix 1 contains the results of the voting for each recommendation, and explains any major individual dissensions. Appendix 2 documents the authors' potential conflicts of interest and industry disclosures.

3) Synopsis of New Recommendations for Blood Conservation

a) Risk Assessment

Not all patients undergoing cardiac procedures have equal risk of bleeding or blood transfusion. An important part of blood resource management is recognition of patients' risk of bleeding and subsequent blood transfusion. In the STS 2007 blood conservation guideline, an extensive review of the literature revealed three broad risk categories for perioperative bleeding or blood transfusion: (1) advanced age, (2) decreased preoperative red blood cell volume (small body size or preoperative anemia or both), and (3) emergent or complex operations (redo procedures, non-CABG operations, aortic surgery, and so forth). Unfortunately, the literature does not provide a good method of assigning relative value to these three risk factors. There is almost no evidence in the literature to stratify blood conservation interventions by patient risk category. Nonetheless, logic suggests that patients at highest risk for bleeding are most likely to benefit from the most aggressive blood management practices, especially since the highest risk patients consume the majority of blood resources.

There is one major risk factor that does not easily fit into any of these three major risk categories, and that is the patient who is unwilling to accept blood transfusion for religious reasons (eg, Jehovah's Witness). Special interventions are available for Jehovah's Witness patients, and the new or revised recommendations include options for these patients. Even within the Jehovah's Witness population, there are differences in willingness to accept blood conservation interventions (see below), so it is an oversimplification to have only one category for this population.

b) Recommendations

Table 1 summarizes the new and revised blood conservation recommendations for patients undergoing cardiac operations based on available evidence. The full text that describes the evidence base behind each of these recommendations is available in the following sections.

Table 2 is a summary of the previously published 2007 guideline recommendations that the writing group feels still have validity and provide meaningful suggestions for blood conservation.

4) Major Changes or Additions

Certain features of blood conservation and management of blood resources stand out based on recently available evidence. Preoperative risk assessment is a necessary starting point. Of the three major preoperative patient risk factors listed above, the patients who are easiest to address are those with low red blood cell volume, either from preoperative anemia or from small body size. Two persistent features of perioperative blood conservation are the need for minimization of hemodilution during CPB and the effective treatment of preoperative anemia. Reduced patient red blood cell volume (fraction of red cells multiplied by blood volume) is a convenient measure of patient risk that correlates with bleeding and blood transfusion in patients with preoperative anemia or small body size. In simplistic terms, red blood cell volume is an index of the red cell reserve that is likely to be depleted by operative intervention. Significant revisions of the blood conservation guidelines aim at reducing hemodilution and conserving preoperative patient red cell volume. These include use of preoperative erythropoietin, minimized CPB circuits with reduced priming volume (minicircuits), normovolemic hemodilution, salvage of blood from the CPB circuit, modified ultrafiltration, and microplegia. Best practice suggests that use of multimodality interventions aimed at preserving red blood cell volume, whether by increasing red cell volume preoperatively with erythrocyte stimulating agents or by limiting hemodilution during operation, offers the best chance of preservation of hemostatic competence and of reduced transfusion.

An equally important part of preoperative risk assessment is identification and management of preoperative antiplatelet and anticoagulant drug therapy. Persistent evidence supports the discontinuation of drugs that inhibit the P2Y12 platelet binding site before operation, but there is wide variability in patient response to drug dosage (especially with clopidogrel). Newer P2Y12 inhibitors are more potent than clopidogrel and differ in their pharmacodynamic properties. Point-of-care testing may

Table 1. New and Revised 2011 Recommendations for Blood Conservation in Patients Undergoing Cardiac Procedures With Differing Risks

Blood Conservation Intervention	Class of Recommendation (Level of Evidence)
Preoperative interventions	
Drugs that inhibit the platelet P2Y12 receptor should be discontinued before operative coronary revascularization (either on pump or off pump), if possible. The interval between drug discontinuation and operation varies depending on the drug pharmacodynamics, but may be as short as 3 days for irreversible inhibitors of the P2Y12 platelet receptor.	I (B)
Point-of-care testing for platelet adenosine diphosphate responsiveness might be reasonable to identify clopidogrel nonresponders who are candidates for early operative coronary revascularization and who may not require a preoperative waiting period after clopidogrel discontinuation.	IIb (C)
Routine addition of P2Y12 inhibitors to aspirin therapy early after coronary artery bypass graft (CABG) may increase the risk of reexploration and subsequent operation and is not indicated based on available evidence except in those patients who satisfy criteria for ACC/AHA guideline-recommended dual antiplatelet therapy (eg, patients presenting with acute coronary syndromes or those receiving recent drug eluting coronary stents).	III (B)
It is reasonable to use preoperative erythropoietin (EPO) plus iron, given several days before cardiac operation, to increase red cell mass in patients with preoperative anemia, in candidates for operation who refuse transfusion (eg, Jehovah's Witness), or in patients who are at high risk for postoperative anemia. However, chronic use of EPO is associated with thrombotic cardiovascular events in renal failure patients suggesting caution for this therapy in individuals at risk for such events (eg, coronary revascularization patients with unstable symptoms).	IIa (B)
Recombinant human erythropoietin (EPO) may be considered to restore red blood cell volume in patients also undergoing autologous preoperative blood donation before cardiac procedures. However, no large-scale safety studies for use of this agent in cardiac surgical patients are available, and must be balanced with the potential risk of thrombotic cardiovascular events (eg, coronary revascularization patients with unstable symptoms).	IIb (A)
Drugs used for intraoperative blood management	
Lysine analogues—epsilon-aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron)—reduce total blood loss and decrease the number of patients who require blood transfusion during cardiac procedures and are indicated for blood conservation.	I (A)
High-dose (Trasylol, 6 million KIU) and low-dose (Trasylol, 1 million KIU) aprotinin reduce the number of adult patients requiring blood transfusion, total blood loss, and reexploration in patients undergoing cardiac surgery but are not indicated for routine blood conservation because the risks outweigh the benefits. High-dose aprotinin administration is associated with a 49% to 53% increased risk of 30-day death and 47% increased risk of renal dysfunction in adult patients. No similar controlled data are available for younger patient populations including infants and children.	III (A)
Blood derivatives used in blood management	
Plasma transfusion is reasonable in patients with serious bleeding in context of multiple or single coagulation factor deficiencies when safer fractionated products are not available.	IIa (B)
For urgent warfarin reversal, administration of prothrombin complex concentrate (PCC) is preferred but plasma transfusion is reasonable when adequate levels of factor VII are not present in PCC.	IIa (B)
Transfusion of plasma may be considered as part of a massive transfusion algorithm in bleeding patients requiring substantial amounts of red-blood cells. (Level of evidence B)	IIb (B)
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.	III (A)
Plasma is not indicated for warfarin reversal in the absence of bleeding.	III (A)
Use of factor XIII may be considered for clot stabilization after cardiac procedures requiring cardiopulmonary bypass when other routine blood conservation measures prove unsatisfactory in bleeding patients.	IIb (C)
When allogeneic blood transfusion is needed, it is reasonable to use leukoreduced donor blood, if available. Benefits of leukoreduction may be more pronounced in patients undergoing cardiac procedures.	IIa (B)
Use of intraoperative platelet plasmapheresis is reasonable to assist with blood conservation strategies as part of a multimodality program in high-risk patients if an adequate platelet yield can be reliably obtained.	IIa (A)
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 cardiopulmonary bypass (CPB).	IIb (B)
Antithrombin III (AT) concentrates are indicated to reduce plasma transfusion in patients with AT mediated heparin resistance immediately before cardiopulmonary bypass.	I (A)
Administration of antithrombin III concentrates is less well established as part of a multidisciplinary blood management protocol in high-risk patients who may have AT depletion or in some, but not all, patients who are unwilling to accept blood products for religious reasons.	IIb (C)

Continued

Table 1. Continued

Blood Conservation Intervention	Class of Recommendation (Level of Evidence)
Use of factor IX concentrates, or combinations of clotting factor complexes that include factor IX, may be considered in patients with hemophilia B or who refuse primary blood component transfusion for religious reasons (eg, Jehovah's Witness) and who require cardiac operations.	IIb (C)
Blood salvage interventions	
In high-risk patients with known malignancy who require CPB, blood salvage using centrifugation of salvaged blood from the operative field may be considered since substantial data supports benefit in patients without malignancy and new evidence suggests worsened outcome when allogeneic transfusion is required in patients with malignancy.	IIb (B)
Consensus suggests that some form of pump salvage and reinfusion of residual pump blood at the end of CPB is reasonable as part of a blood management program to minimize blood transfusion.	IIa (C)
Centrifugation of pump-salvaged blood, instead of direct infusion, is reasonable for minimizing post-CPB allogeneic red blood cell (RBC) transfusion.	IIa (A)
Minimally invasive procedures	
Thoracic endovascular aortic repair (TEVAR) of descending aortic pathology reduces bleeding and blood transfusion compared with open procedures and is indicated in selected patients.	I (B)
Off-pump operative coronary revascularization (OPCABG) is a reasonable means of blood conservation, provided that emergent conversion to on-pump CABG is unlikely and the increased risk of graft closure is considered in weighing risks and benefits.	IIa (A)
Perfusion interventions	
Routine use of a microplegia technique may be considered to minimize the volume of crystalloid cardioplegia administered as part of a multimodality blood conservation program, especially in fluid overload conditions like congestive heart failure. However, compared with 4:1 conventional blood cardioplegia, microplegia does not significantly impact RBC exposure.	IIb (B)
Extracorporeal membrane oxygenation (ECMO) patients with heparin-induced thrombocytopenia should be anticoagulated using alternate nonheparin anticoagulant therapies such as danaparoid or direct thrombin inhibitors (eg, lepirudin, bivalirudin or argatroban).	I (C)
Minicircuits (reduced priming volume in the minimized CPB circuit) reduce hemodilution and are indicated for blood conservation, especially in patients at high risk for adverse effects of hemodilution (eg, pediatric patients and Jehovah's Witness patients).	I (A)
Vacuum-assisted venous drainage in conjunction with minicircuits may prove useful in limiting bleeding and blood transfusion as part of a multimodality blood conservation program.	IIb (C)
Use of biocompatible CPB circuits may be considered as part of a multimodality program for blood conservation.	IIb (A)
Use of modified ultrafiltration is indicated for blood conservation and reducing postoperative blood loss in adult and pediatric cardiac operations using CPB.	I (A)
Benefit of the use of conventional or zero balance ultrafiltration is not well established for blood conservation and reducing postoperative blood loss in adult cardiac operations.	IIb (A)
Available leukocyte filters placed on the CPB circuit for leukocyte depletion are not indicated for perioperative blood conservation and may prove harmful by activating leukocytes during CPB.	III (B)
Topical hemostatic agents	
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.	IIb (C)
Antifibrinolytic agents poured into the surgical wound after CPB are reasonable interventions to limit chest tube drainage and transfusion requirements after cardiac operations using CPB.	IIa (B)
Management of blood resources	
Creation of multidisciplinary blood management teams (including surgeons, perfusionists, nurses, anesthesiologists, intensive care unit care providers, housestaff, blood bankers, cardiologists, etc.) is a reasonable means of limiting blood transfusion and decreasing perioperative bleeding while maintaining safe outcomes.	IIa (B)

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

help identify patients with incomplete drug response who can safely undergo urgent operations.

There is no substitute for good operative technique, but new evidence suggests that adjunctive topical interventions that supplement local hemostasis are reasonable. An emerging body of literature suggests that topical agents, especially topical antifibrinolytic agents, limit bleeding in the surgical wound. These agents are especially important since abnormalities in postoperative hemostasis start with activation of tissue factor and factor VII in the surgical wound [10]. Topical agents can potentially interrupt the cascade of hemostatic abnormalities closer to the source as opposed to replacement therapy added after the hemostatic insult has occurred.

Table 2. Recommendations From Previously Published Blood Conservation Guidelines With Persistent Support in the Current Medical Literature [9]

Recommendation	Class
Preoperative interventions	
Preoperative identification of high-risk patients (advanced age, preoperative anemia, small body size, noncoronary artery bypass graft or urgent operation, preoperative antithrombotic drugs, acquired or congenital coagulation/clotting abnormalities and multiple patient comorbidities) 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. (Level of evidence A)	I
Preoperative hematocrit and platelet count are indicated for risk prediction and abnormalities in these variables are amenable to intervention. (Level of evidence A)	I
Preoperative screening of the intrinsic coagulation system is not recommended unless there is a clinical history of bleeding diathesis. (Level of evidence B)	III
Patients who have thrombocytopenia (<50,000/mm^2), who are hyperresponsive to aspirin or other antiplatelet drugs as manifested by abnormal platelet function tests or prolonged bleeding time, or who have known qualitative platelet defects represent a high-risk group for bleeding. Maximum blood conservation interventions during cardiac procedures are reasonable in these high-risk patients. (Level of evidence B)	IIa
It is reasonable to discontinue low-intensity antiplatelet drugs (eg, aspirin) only in purely elective patients without acute coronary syndromes before operation with the expectation that blood transfusion will be reduced. (Level of evidence A)	IIa
Most high-intensity antithrombotic and antiplatelet drugs (including adenosine diphosphate-receptor inhibitors, direct thrombin inhibitors, low molecular weight heparins, platelet glycoprotein inhibitors, tissue-type plasminogen activator, streptokinase) are associated with increased bleeding after cardiac operations. Discontinuation of these medications before operation may be considered to decrease minor and major bleeding events. The timing of discontinuation depends on the pharmacodynamic half-life for each agent as well as the potential lack of reversibility. Unfractionated heparin is the notable exception to this recommendation and is the only agent which either requires discontinuation shortly before operation or not at all. (Level of evidence C)	IIb
Alternatives to laboratory blood sampling (eg, oximetry instead of arterial blood gasses) are reasonable means of blood conservation before operation. (Level of evidence B)	IIa
Screening preoperative bleeding time may be considered in high-risk patients, especially those who receive preoperative antiplatelet drugs. (Level of evidence B)	IIb
Devices aimed at obtaining direct hemostasis at catheterization access sites may be considered for blood conservation if operation is planned within 24 hours. (Level of evidence C)	IIb
Transfusion triggers	
Given that the risk of transmission of known viral diseases with blood transfusion is currently rare, fears of viral disease transmission should not limit administration of INDICATED blood products. (This recommendation only applies to countries/blood banks where careful blood screening exists.) (Level of evidence C)	IIa
Transfusion is unlikely to improve oxygen transport when the hemoglobin concentration is greater than 10 g/dL and is not recommended. (Level of evidence C)	III
With hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable since this can be life-saving. Transfusion is reasonable in most postoperative patients whose hemoglobin is less than 7 g/dL but no high level evidence supports this recommendation. (Level of evidence C)	IIa
It is reasonable to transfuse nonred-cell hemostatic blood products based on clinical evidence of bleeding and preferably guided by point-of-care tests that assess hemostatic function in a timely and accurate manner. (Level of evidence C)	IIa
During cardiopulmonary bypass (CPB) with moderate hypothermia, transfusion of red cells for hemoglobin ≤6 g/dL is reasonable except in patients at risk for decreased cerebral oxygen delivery (ie, history of cerebrovascular attack, diabetes, cerebrovascular disease, carotid stenosis) where higher hemoglobin levels may be justified. (Level of evidence C)	IIa
In the setting of hemoglobin values exceeding 6 g/dL while on CPB, it is reasonable to transfuse red cells based on the patient's clinical situation, and this should be considered as the most important component of the decision making process. Indications for transfusion of red blood cells in this setting are multifactorial and should be guided by patient-related factors (ie, age, severity of illness, cardiac function, or risk for critical end-organ ischemia), the clinical setting (massive or active blood loss), and laboratory or clinical parameters (eg, hematocrit, SVO_2, electrocardiogram, or echocardiographic evidence of myocardial ischemia etc.). (Level of evidence C)	IIa
It is reasonable to transfuse nonred-cell hemostatic blood products based on clinical evidence of bleeding and preferably guided by specific point-of-care tests that assess hemostatic function in a timely and accurate manner. (Level of evidence C)	IIa
It may be reasonable to transfuse red cells in certain patients with critical noncardiac end-organ ischemia (eg, central nervous system and gut) whose hemoglobin levels are as high as 10 g/dL but more evidence to support this recommendation is required. (Level of evidence C)	IIb
In patients on CPB with risk for critical end-organ ischemia/injury, transfusion to keep the hemoglobin ≥ 7 g/dL may be considered. (Level of evidence C)	IIb
Drugs used for intraoperative blood management	
Use of 1-deamino-8-D-arginine vasopressin (DDAVP) may be reasonable to attenuate excessive bleeding and transfusion in certain patients with demonstrable and specific platelet dysfunction known to respond to this agent (eg, uremic or CPB-induced platelet dysfunction, type I von Willebrand's disease). (Level of evidence B)	IIb

Continued

Table 2. Continued

Recommendation	Class
Routine prophylactic use of DDAVP is not recommended to reduce bleeding or blood transfusion after cardiac operations using CPB. (Level of evidence A)	III
Dipyridamole is not indicated to reduce postoperative bleeding, is unnecessary to prevent graft occlusion after coronary artery bypass grafting, and may increase bleeding risk unnecessarily. (Level of evidence B)	III
Blood salvage interventions	
Routine use of red cell salvage using centrifugation is helpful for blood conservation in cardiac operations using CPB. (Level of evidence A)	I
During CPB, intraoperative autotransfusion, either with blood directly from cardiotomy suction or recycled using centrifugation to concentrate red cells, may be considered as part of a blood conservation program. (Level of evidence C)	IIb
Postoperative mediastinal shed blood reinfusion using mediastinal blood processed by centrifugation may be considered for blood conservation when used in conjunction with other blood conservation interventions. Washing of shed mediastinal blood may decrease lipid emboli, decrease the concentration of inflammatory cytokines, and reinfusion of washed blood may be reasonable to limit blood transfusion as part of a multimodality blood conservation program. (Level of evidence B)	IIb
Direct reinfusion of shed mediastinal blood from postoperative chest tube drainage is not recommended as a means of blood conservation and may cause harm. (Level of evidence B)	III
Perfusion interventions	
Open venous reservoir membrane oxygenator systems during cardiopulmonary bypass may be considered for reduction in blood utilization and improved safety. (Level of evidence C)	IIb
All commercially available blood pumps provide acceptable blood conservation during CPB. It may be preferable to use centrifugal pumps because of perfusion safety features. (Level of evidence B)	IIb
In patients requiring longer CPB times (>2 to 3 hours), maintenance of higher and/or patient-specific heparin concentrations during CPB may be considered to reduce hemostatic system activation, reduce consumption of platelets and coagulation proteins, and to reduce blood transfusion. (Level of evidence B)	IIb
Use either protamine titration or empiric low dose regimens (eg, 50% of total heparin dose) to lower the total protamine dose and lower the protamine/heparin ratio at the end of CPB may be considered to reduce bleeding and blood transfusion requirements. (Level of evidence B)	IIb
The usefulness of low doses of systemic heparinization (activated clotting time ~300 s) is less well established for blood conservation during CPB but the possibility of underheparinization and other safety concerns have not been well studied. (Level of evidence B)	IIb
Acute normovolemic hemodilution may be considered for blood conservation but its usefulness is not well established. It could be used as part of a multipronged approach to blood conservation. (Level of evidence B)	IIb
Retrograde autologous priming of the CPB circuit may be considered for blood conservation. (Level of evidence B)	IIb
Postoperative care	
A trial of therapeutic positive end-expiratory pressure (PEEP) to reduce excessive postoperative bleeding is less well established. (Level of evidence B)	IIb
Use of prophylactic PEEP to reduce bleeding postoperatively is not effective. (Level Evidence B)	III
Management of blood resources	
A multidisciplinary approach involving multiple stakeholders, institutional support, enforceable transfusion algorithms supplemented with point-of-care testing, and all of the already mentioned efficacious blood conservation interventions limits blood transfusion and provides optimal blood conservation for cardiac operations. (Level of evidence A)	I
A comprehensive integrated, multimodality blood conservation program, using evidence based interventions in the intensive care unit, is a reasonable means to limit blood transfusion. (Level of evidence B)	IIa
Total quality management, including continuous measurement and analysis of blood conservation interventions as well as assessment of new blood conservation techniques, is reasonable to implement a complete blood conservation program. (Level of evidence B)	IIa

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Minimally invasive procedures, especially implantation of aortic endografts, offer significant savings in blood product utilization. Implantation of aortic endografts for aortic disease is a major advance in blood conservation for a very complex and high-risk group of patients. Similarly, a body of evidence suggests that off-pump procedures limit bleeding and blood transfusion in a select group of patients undergoing coronary revascularization without the use of CPB (OPCABG). However, because of concerns about graft patency in OPCABG procedures [11], the body of evidence to support routine OPCABG for blood conservation during coronary revascularization is not as robust as for aortic endografts.

Finally, the management of blood resources is an important component of blood conservation. Evidence suggests that a multidisciplinary team made up of a broad base of stakeholders provides better utilization of blood resources, while preserving quality outcomes, than does a single decision maker who makes transfusion decisions about blood conservation in bleeding patients. Many decisions about transfusion are not made by surgeons. Recognizing the multitude of practitioners who participate in the transfusion decision is an important step in managing valuable blood resources. Evidence suggests that teams make better decisions about blood transfusion than do individuals. Furthermore, massive

bleeding is life-threatening and should prompt incorporation of expert team members to improve outcomes [12]. Likewise, publications continue to suggest that definition of a consistent transfusion algorithm to which all team members agree and use of point-of-care testing to guide transfusion decisions are important components of blood resource management.

5) Evidence Supporting Guideline Recommendations

a) Preoperative Interventions

DUAL ANTIPLATELET THERAPY

Class I.

1. Drugs that inhibit the platelet P2Y12 receptor should be discontinued before operative coronary revascularization (either on-pump or off-pump), if possible. The interval between drug discontinuation and operation varies depending on the drug pharmacodynamics, but may be as short as 3 days for irreversible inhibitors of the P2Y12 platelet receptor. (Level of evidence B)

Class IIb.

1. Point-of-care testing for platelet ADP responsiveness might be reasonable to identify clopidogrel nonresponders who are candidates for early operative coronary revascularization and who may not require a preoperative waiting period after clopidogrel discontinuation. (Level of evidence C)

Class III.

1. Routine addition of P2Y12 inhibitors to aspirin therapy early after CABG may increase the risk of reexploration and subsequent operation and is not indicated based on available evidence except in those patients who satisfy criteria for ACC/AHA guideline-recommended dual antiplatelet therapy (eg, patients presenting with acute coronary syndromes or those receiving recent drug eluting coronary stents). (Level of evidence B)

Our previous review of the literature found at least six risk factors in patients who bleed excessively after cardiac procedures and require excess transfusion: 1) advanced age, 2) low red blood cell volume (either from preoperative anemia or from low body mass), 3) preoperative anticoagulation or antiplatelet therapy, 4) urgent or emergent operation, 5) anticipated prolonged duration of cardiopulmonary bypass, and 6) certain comorbidities (eg, congestive heart failure, renal dysfunction, and chronic obstructive pulmonary disease) [9]. Active preoperative intervention is most likely to reduce risk in only two of these risk factors—modification of preoperative anticoagulant or antiplatelet regimens and increasing red blood cell volume.

Preoperative P2Y12 platelet inhibitors are commonly used drugs in patients with acute coronary syndromes and are a likely site for intervention to decrease bleeding risk in CABG patients. Abundant evidence (mostly Level B small retrospective nonrandomized studies) suggests that clopidogrel is associated with excessive perioperative bleeding in patients requiring CABG [13, 14]. Off-pump procedures do not seem to lessen this risk [15, 16]. Whether or not excessive bleeding in CABG patients treated with preoperative dual antiplatelet therapy translates into adverse outcomes is less certain. A recent reevaluation of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial data found that dual antiplatelet therapy (clopidogrel plus aspirin) administered before catheterization in patients with acute coronary syndromes who subsequently require CABG was associated with significantly fewer adverse ischemic events without significantly increased bleeding compared with withholding clopidogrel until after catheterization [17]. This desirable outcome occurred with adherence to a policy of withholding clopidogrel for up to 5 days before operation whenever possible. So it may be that the net benefit of dual antiplatelet therapy overshadows the excess bleeding risk but evidence (mostly Level B) suggests that, where possible, a policy of delaying operation for a period of time reduces the bleeding risk and is the best option.

Previous reports recommended 5- to 7-day delay after discontinuation of clopidogrel in patients requiring CABG. Two recent studies suggest that a 3-day delay may be an alternative to lessen bleeding risk and provide safe outcomes [15,18]. Furthermore, most surgeons do not wait the recommended 5 to 7 days before proceeding with operation [19]. It is likely that a 5- to 7-day delay is not necessary but some period of discontinuation of clopidogrel is supported by available evidence.

An interesting misunderstanding between cardiologists and cardiac surgeons limits discussions about use of antiplatelet drugs around the time of operation. Aspirin causes approximately a 30% to 40% reduction in ischemic events in patients with acute coronary syndromes (ACS) [20, 21]. Another way of saying this, that has meaning to surgeons, is that treating 100 patients who have ACS with aspirin results in 10 to 12 fewer ischemic events compared with no aspirin therapy—namely, a decrease in ischemic events from 22% in controls to 12% in aspirin-only treated patients at 1 year after the acute event. Adding clopidogrel to aspirin results in a 20% relative risk reduction or about 2 to 3 fewer ischemic events per 100 ACS patients [14]. The added risk of bleeding related to preoperative clopidogrel in CABG patients exposes 70% of CABG patients (assuming 30% clopidogrel resistance) to the risk of bleeding but only benefits, at most, 2 to 3 patients per 100 at 1 year after operation. Not all CABG patients exposed to preoperative dual antiplatelet therapy experience increased bleeding or blood transfusion but there is likely more than a 50% increase in the relative risk of the combined endpoint of reoperation for bleeding and increased blood transfusion related to the addition of clopidogrel—for example, 40% combined bleeding endpoint in dual antiplatelet treated patients compared with 30% in aspirin-only treated patients. This suggests that 10 patients in 100 may benefit from discon-

tinuation of clopidogrel in the short period around the time of operation. There is almost no information about the effect of short-term or intermittent cessation of antiplatelet drugs on 1 year thrombotic outcomes. These calculations are approximate but illustrate the point. Aspirin benefit in ACS patients is roughly twice that of added clopidogrel, and continuation of aspirin, and discontinuation of clopidogrel, in ACS patients provides a reasonable risk-benefit relationship in surgical patients [22]. To surgeons, the added risk of clopidogrel exposes 70% of CABG patients to the risk of bleeding but only benefits, at most, 2 to 3 patients per 100 at 1 year.

At least two new P2Y12 inhibitors are available for clinical use [23, 24]. Both of these new agents have different pharmacodynamic properties than clopidogrel. Each new drug has quicker onset of action and shorter half-life in the blood stream. Both are more potent inhibitors of the platelet P2Y12 receptor. Importantly, one of these new drugs is a reversible inhibitor of the P2Y12 receptor as opposed to clopidogrel and prasugrel, which inhibit these receptors for the lifetime of the platelet. The expected result of these differing properties is increased efficacy at the expense of increased bleeding. A word of caution is necessary in reading reports about bleeding associated with these new P2Y12 inhibitors. Most large cardiology studies report TIMI (Thrombolysis in Myocardial Infarction) bleeding, which does not take into account bleeding associated with CABG. So even though studies report no excess TIMI bleeding with newer agents, there is still excess bleeding associated with CABG [24].

There is variability in response to antiplatelet therapy, and patients who have higher levels of platelet reactivity after drug ingestion are at increased risk for recurrent ischemic events [25]. As many as 30% of patients are resistant to clopidogrel and 10% to 12% may have drug resistance to the aspirin/clopidogrel combination [26–28]. There are many possible reasons for drug resistance including genetic variability [29, 30] and lack of drug compliance [31]. The lack of a consistent definition of inadequate platelet response, as well as the lack of a standardized measurement technique, makes it difficult to define optimal treatment in these patients.

Point-of-care tests are available to measure platelet ADP responsiveness. These tests are not perfect [32–34]. They lack sensitivity and specificity. Nonetheless, point-of-care tests that indicate normal platelet ADP responsiveness after administration of a loading dose of clopidogrel suggest P2Y12 resistance with as much as 85% specificity [32, 34]. More accurate tests are available but are not point-of-care tests [32, 35].

Aspirin limits vein graft occlusion after CABG. A logical extension of this concept is to add clopidogrel or other P2Y12 inhibitors to aspirin therapy after CABG to reduce cardiac events after operation and to improve vein graft patency. A systematic review of this subject appeared in the literature [36]. Two small prospective trials providing data on surrogate endpoints, and five small trials involving off-pump CABG patients were not of good quality to draw meaningful conclusions. A summary of the data based on subgroup analyses, surrogate endpoints, and observational cohort studies failed to demonstrate a beneficial effect of clopidogrel alone or in combination with aspirin on clinical outcomes after CABG, and this therapy cannot be recommended until further high-level evidence is available [16]. Addition of P2Y12 inhibitors after operation risks subsequent bleeding should reoperation be necessary for any reason. After CABG, resistance to antiplatelet drugs, either aspirin or P2Y12 inhibitors, is an independent predictor of adverse outcomes [37]. It is likely that antiplatelet drug resistance contributes to thrombotic events and graft occlusion after CABG, but arbitrary administration of additional antiplatelet agents is not a reliable means of addressing this issue.

SHORT-COURSE ERYTHROPOIETIN

Class IIa.

1. It is reasonable to use preoperative erythropoietin (EPO) plus iron, given several days before cardiac operation, to increase red cell mass in patients with preoperative anemia, in candidates for operation who refuse transfusion (eg, Jehovah's Witness), or in patients who are at high risk for postoperative anemia. However, chronic use of EPO is associated with thrombotic cardiovascular events in renal failure patients suggesting caution for this therapy in persons at risk for such events (eg, coronary revascularization patients with unstable symptoms). (Level of evidence B)

Class IIb.

1. Recombinant human EPO may be considered to restore red blood cell volume in patients also undergoing autologous preoperative blood donation before cardiac procedures. However, no large-scale safety studies for use of this agent in cardiac surgical patients are available, and must be balanced with the potential risk of thrombotic cardiovascular events (eg, coronary revascularization patients with unstable symptoms). (Level of evidence A)

Erythropoietin is an endogenous glycoprotein hormone that stimulates red blood cell production in response to tissue hypoxia and anemia. Endogenous EPO is primarily produced by the kidney, so its production is significantly diminished in patients with impaired renal function. Recombinant human EPO, developed in the mid 1980s, is commercially available in several forms. Guidelines for EPO use to treat anemia in renal failure patients lowered recommended hemoglobin target levels from 13 g/dL to 11 to 12 g/dL. These changes occurred because of concerns about the increased incidence of thrombotic cardiovascular events and a trend towards increased mortality in a meta-analysis of 14 trials including more than 4,000 patients [38]. Whether these more conservative target hemoglobin values apply to patients given a short preoperative course of EPO is uncertain. However, these guidelines are particularly relevant in

patients at risk for thrombotic complications (eg, coronary and carotid revascularization procedures) [39, 40].

A body of evidence, including four meta-analyses [41–44], supports the preoperative administration of EPO to reduce the preoperative anemia in adults [45–48] and children [49, 50] having autologous blood donation. Evidence for efficacy with the preoperative use of EPO in anemic patients (hemoglobin ≤13 g/dL) without autologous predonation is less compelling, but still supportive. Most literature supporting the use of EPO to reduce preoperative anemia is anecdotal, but it does outline successful case reports in a handful of patients, particularly for Jehovah's Witnesses, where the risk/benefit ratio may be particularly favorable [41, 51–57].

Although the safety of perioperative EPO therapy is incompletely understood, the risk for thromboembolic events must be weighed against the benefit of reduced transfusion. Erythropoietin is effective for the improvement of preoperative anemia, with the main side effect being hypertension. Of particular importance, adequate iron supplementation is required in conjunction with EPO to achieve the desired red blood cell response. A typical preoperative regimen of EPO is costly. Uncertainty still exists about the cost-effectiveness of EPO in patients undergoing autologous blood donation before cardiac procedures.

Preoperative anemia is associated with operative mortality and morbidity in cardiac procedures [58]. Therefore, it is possible that EPO therapy for more than 1 week before operation may reduce adverse outcomes by augmenting red cell mass in anemic patients treated with iron. This recommendation is based on limited evidence and consensus [59]. No large-scale safety studies exist in patients having cardiac procedures, so such use must be considered "off label' and incompletely studied. In patients with unstable angina, there is limited support for the use of preoperative EPO as these patients may be most prone to thrombotic complications. Preoperative interventions using EPO seem justified in elective patients with diminished red cell mass because of the high risk of excessive blood transfusion in this subset.

Still fewer objective data are available regarding the use of EPO to treat perioperative and postoperative anemia. Because the onset of action of the drug is 4 to 6 days, it is necessary to administer EPO a few days in advance of operation, a luxury that is not always possible. Limited evidence and consensus supports the addition of EPO to patients expected to have a large blood loss during operation or who are anemic preoperatively [59]. Similar benefit occurs in off-pump procedures done in mildly anemic patients [59]. Other considerations for the use of EPO include situations in which endogenous EPO production is limited. For instance, beta-blockers suppress endogenous EPO production [60], and surgical anemia decreases the cardioprotective effect of beta-blockade [61]. Additionally, cytokines stimulated by the inflammatory response associated with CPB limit production of EPO [62]. 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 EPO (a few days before operation) to treat reduced red blood cell volume in selected individual patients.

b) Drugs Used for Intraoperative Blood Management

DRUGS WITH ANTIFIBRINOLYTIC PROPERTIES

Class I.

1. Lysine analogues—epsilon-aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron)—reduce total blood loss and decrease the number of patients who require blood transfusion during cardiac procedures and are indicated for blood conservation. (Level of evidence A)

Class III.

1. High-dose aprotinin (Trasylol, 6 million KIU) reduces the number of adult patients requiring blood transfusion, total blood loss, and reexploration in patients undergoing cardiac surgery but is not indicated for routine blood conservation because the risks outweigh the benefits. High-dose aprotinin administration is associated with a 49% to 53% increased risk of 30-day death and 47% increased risk of renal dysfunction in adult patients. No similar controlled data are available for other patient populations including infants and children. (Level of evidence A)
2. Low-dose aprotinin (Trasylol, 1 million KIU) reduces the number of adult patients requiring blood transfusion and total blood loss in patients having cardiac procedures, but risks outweigh the benefits and this drug dosage should not be used for low or moderate risk patients. (Level of evidence B)

The wide-spread adoption of antifibrinolytic therapies for cardiac surgery stimulated concern over the safety and efficacy of these drugs [38, 63–69]. After the publication of the BART (Blood Conservation Using Antifibrinolytics) trial on May 14, 2008, the manufacturer of aprotinin (Bayer) informed the Food and Drug Administration (FDA) of their intent to remove all stocks of Trasylol (aprotinin) from hospitals and warehouses [38]. The BART study was the first large scale head-to-head trial comparing aprotinin with lysine analogs tranexamic acid and epsilon-aminocaproic acid reporting a significant increased risk of 30-day death among patients randomly assigned to aprotinin compared with lysine analogues (relative risk [RR] 1.53; 95% confidence interval [CI]: 1.06 to 2.22) [65]. As a result of recent randomized trials and supporting evidence from meta-analyses and postmarketing data from the FDA recommendations for drugs with antifibrinolytic properties require revision.

In 2009, the Cochran collaborative updated its meta-analysis on aprotinin use in all types of surgery showing higher rates of death for aprotinin compared with tranexamic acid (RR 1.43; 95% CI: 0.98 to 2.08) and epsilon-aminocaproic acid (RR 1.49; 95% CI: 0.98 to 2.28)

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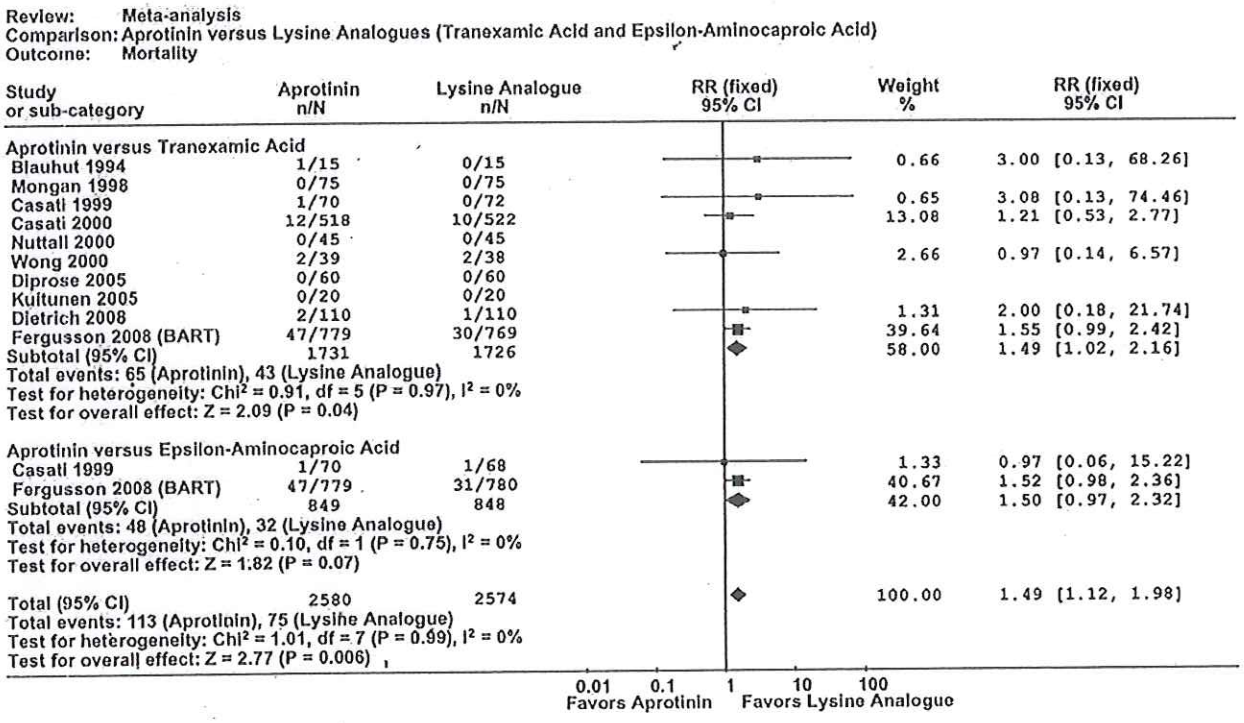

Fig 1. Meta-analysis comparing mortality between aprotinin and tranexamic acid or epsilon aminocarpoic acid. The relative risks (RR) of mortality by antifibrinolytic agent compared head-to-head are plotted. The RR for each study is plotted (blue box) with 95% confidence interval (horizontal bar). A pooled estimate RR (diamond) and 95% confidence intervals (width of diamonds) summarize the effect using a fixed effects model. Effects to the left of 1.0 favors aprotinin over tranexamic acid or epsilon aminocaproic acid; effects to the right favors tranexamic acid or epsilon aminocaproic acid over aprotinin. When the horizontal bars cross 1.0, the effect is not significantly different from the comparison group. The I^2 test for heterogeneity was not significant, demonstrating homogeneity in mortality effects across the independent randomized trials (a trend toward increased death risk with aprotinin treatment).

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[66]. Figure 1 shows a summary of the head-to-head comparisons between aprotinin and lysine analogues. Aprotinin carries a significant increased risk of death up to 30 days after operation compared with tranexamic acid (RR 1.49; 95% CI: 1.02 to 2.16) and a similar effect with epsilon-aminocaproic acid (RR 1.50; 95% CI: 0.97 to 2.32). By pooling the mortality results, there is a significant increased mortality (RR 1.49, 95% CI:1.12 to 1.98) with aprotinin (4.4%) compared with lysine analogues (2.9%). The randomized trial data and meta-analyses support the FDA analysis of the i3 Drug Safety Study of 135,611 patients revealing an increased adjusted risk of death (RR 1.54; 95% CI: 1.38 to 1.73), stroke (RR 1.24; 95% CI: 1.07 to 1.44), renal failure (RR 1.82; 95% CI: 1.61 to 2.06), and heart failure (RR 1.20; 95% CI: 1.14 to 1.26) [70]. Because of these safety concerns, risks of aprotinin outweigh the benefits, and its routine use in low to moderate risk cardiac operations is not recommended.

Since discontinued use of aprotinin occurred abruptly in the United States in 2008, comparisons of bleeding risk before and after aprotinin availability appeared in the literature [71–73]. Some of these studies suggest that blood product transfusion increased after aprotinin disappeared from clinical use, but others do not. New reports suggested benefit from aprotinin in reducing blood transfusion without significant increased risk. Aprotinin may be beneficial in infants [74,75], and in patients at greatest risk for postoperative bleeding [76]. Aprotinin reduces the need for blood transfusion in cardiac operations by about 40% [73], and this benefit may be substantially greater in the patients at highest risk for bleeding [76]. Aprotinin availability is limited in many countries including the United States, except for compassionate and special circumstances. It remains for the clinician and patient to determine the risk benefit profile for use of this drug in cardiac operations. The highest risk patients and in those patients with no blood transfusion alternatives (ie, Jehovah's Witness) may be potential candidates for use of aprotinin, but usage in this setting is likely to be rare. Since the abrupt discontinuation of aprotinin in the United States, further cautionary reports appeared in the literature [77]. Aprotinin is still used in fibrin sealant preparations, and anaphylactic reactions occur in this setting [78].

Case reports and cohort studies identified a possible risk of seizure after the injection of tranexamic acid during cardiac procedures [79]. However, a subsequent randomized trial did not confirm this finding [80]. An upcoming trial (Aspirin and Tranexamic Acid for Coronary Artery Surgery trial) enrolling 4,600 patients may provide

answers about the safety profile of this drug [81]. Large-scale head-to-head randomized trials and postmarketing surveillance identify potentially harmful side effects and this information is incomplete for lysine analogs, despite approval of these agents by regulatory organizations.

c) Blood Derivatives Used for Blood Conservation

PLASMA TRANSFUSION

Class IIa.

1. Plasma transfusion is reasonable in patients with serious bleeding in context of multiple or single coagulation factor deficiencies when safer fractionated products are not available. (Level of evidence B)
2. For urgent warfarin reversal, administration of prothrombin complex concentrate (PCC) is preferred, but plasma transfusion is reasonable when adequate levels of Factor VII are not present in PCC. (Level of evidence B)

Class IIb.

1. Transfusion of plasma may be considered as part of a massive transfusion algorithm in bleeding patients requiring substantial amounts of red-blood cells. (Level of evidence B)

Class III.

1. 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. (Level of evidence A)
2. Plasma is not indicated for warfarin reversal or treatment of elevated international normalized ratio in the absence of bleeding. (Level of evidence A)

Plasma transfusions share many of the risks and complications associated with RBC transfusions. Some risks of blood product transfusion (eg, transfusion-related acute lung injury) are specifically linked to plasma transfusions. Moreover, the same cost and logistic challenges faced by other blood components plague plasma transfusions as well. Therefore, reduction or avoidance of plasma transfusions should be among objectives of blood conservation strategies.

Similar to other blood components, substantial variations exist in the plasma transfusion practices in general and specifically in cardiac surgery, with many centers not following any available guidelines [82, 83]. Conversely, available guidelines are dated and often based on limited low-quality evidence and do not specifically address cardiac surgery [84, 85].

Current clinical indications for plasma are mainly limited to serious bleeding or surgical procedures in the context of multiple or single coagulation factor deficiencies when safer fractionated products are not available [85–87]. Factor deficiencies that justify plasma transfusion can be congenital, acquired, dilutional, or due to consumption (disseminated intravascular coagulation), but usually occur in the presence of serious bleeding [84, 87]. In patients with microvascular bleeding after CPB, plasma may limit coagulopathy [88].

Prothrombin complex concentrate (PCC) is preferred for reversing warfarin. Plasma should not be considered for warfarin reversal unless PCC is not available and/or severe bleeding is present [89–91]. The PCC contains relatively high levels of factors II, IX, and X, and in some preparations, factor VII (see below). Compared with plasma, PCC is administered in much smaller volumes without consideration of blood groups, is free of many safety issues of plasma as an allogeneic blood component, and acts faster. Recent evidence suggests that PCC can be used in bleeding patients without coagulopathy, but more evidence is needed to establish this as an indication in bleeding patients undergoing cardiac operations [92]. Prothrombin complex concentrate poses some thrombotic risks, usually in patients with other prothrombotic risk factors [93]. Information regarding thrombotic risks in patients having cardiac operations is lacking. It should be noted that current PCC preparations available in the United States contain reduced or negligible amounts of factor VII compared with the PCC units available in Europe possibly reducing their effectiveness in warfarin reversal [94, 95].

Approximately one fifth of patients undergoing CPB have an inadequate response to heparin, a condition known as heparin resistance. Fresh frozen plasma (FFP) may be used to treat heparin resistance, but antithrombin concentrate is preferred since there is reduced risk of transmitting infections and other blood complications and antithrombin concentrate does not result in volume overload (see below) [96].

Plasma units are commonly included in massive transfusion protocols. Although some studies indicate better outcomes with higher FFP:RBC ratios, conflicting reports exist on the benefits of FFP in this context. The presence of a survival bias resulting in apparent beneficial effect of FFP cannot be ruled out [97–100]. Plasma is not useful for volume expansion, plasma exchange (with possible exception of thrombotic thrombocytopenic purpura), or correction of coagulopathy in the absence of bleeding [85].

Available evidence does not support prophylactic use of plasma transfusion as part of blood conservation strategies, in the absence of the above evidence-based indications. A systemic review of six clinical trials including a total of 363 patients undergoing cardiac procedures showed no improvement in blood conservation with prophylactic use of plasma [101]. Importantly, significant heterogeneity exists in the studies included in this analysis. Differences in controls used for these studies and in the type of plasma included in the experimental groups (allogeneic FFP versus autologous plasma) account for this heterogeneity. Another review identified seven additional randomized trials of FFP used in cardiovascular procedures (including pediatric operations), and found no association between use of FFP and reduced surgical blood loss [102]. These reviews contain several methodological limitations, but constitute the only available evidence to address the use of plasma in cardiac procedures [102].

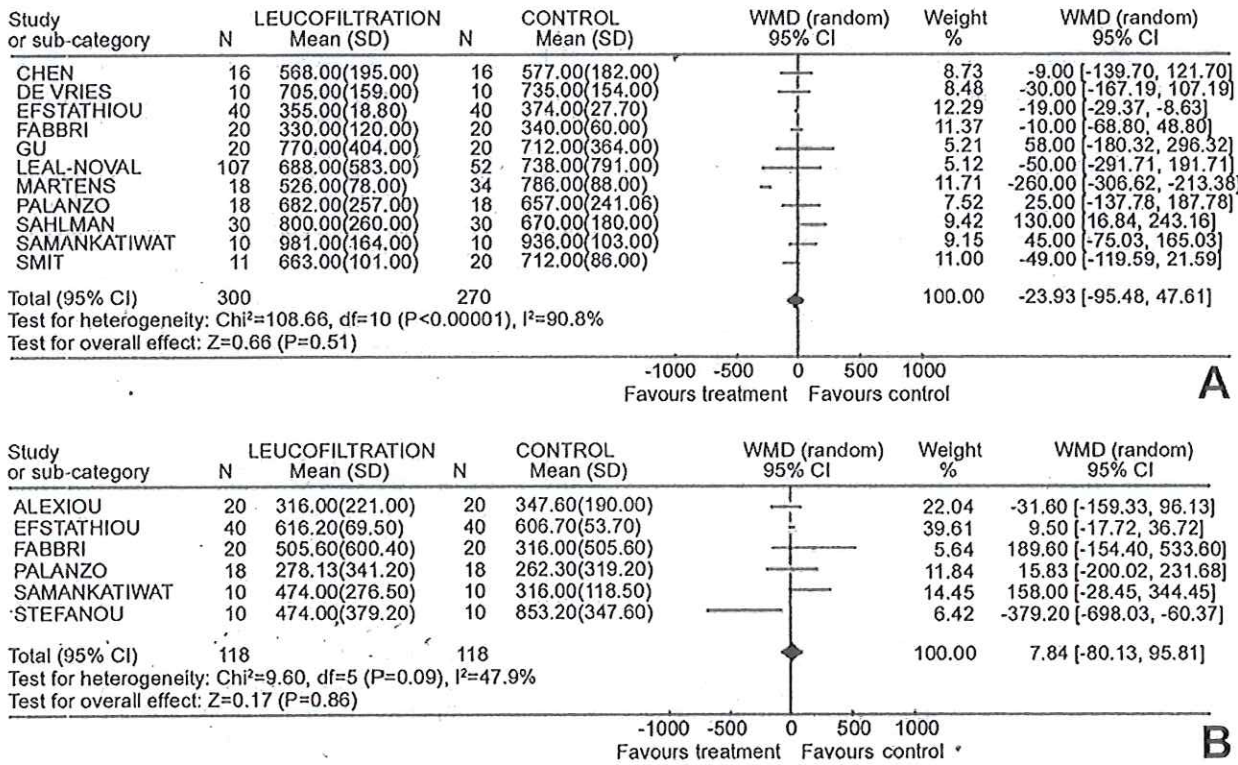

Fig 2. Forest plot displaying (A) the 24-hour chest tube drainage and (B) packed red cell transfusion requirement in patients undergoing cardiopulmonary bypass with standard filters (control) compared with leukodepletion filters. (Reprinted from Warren O, et al, ASAIO J 2007;53: 514-21 [139], with permission.)

Trials that examined use of FFP in cardiac operations suffer from small sample size and lack of modern-day perspective. Consten et al conducted a more contemporary study that evaluated 50 elective CPB patients (mean age 63 years; 70% male) who were randomly assigned to receive 3 units of FFP after operation or an equal amount of Gelofusine plasma substitute [103]. They found no significant differences between the two study groups with regard to blood loss, transfusion requirement, coagulation variables, or platelet counts. In contrast, Kasper and associates [104] randomly assigned 60 patients undergoing elective primary CABG to receive 15 mL/kg autologous FFP (obtained by platelet-poor plasmapheresis several weeks before surgery) or 15 mL/kg of 6% hydroxyethyl starch 450/0.7 after CPB, and noted that postoperative and total perioperative RBC transfusion requirements were not different between the two groups. In another study, Wilhelmi and colleagues [105] compared 60 patients undergoing elective CABG surgery who received 4 units of FFP intraoperatively with 60 controls who did not receive FFP, and demonstrated that avoidance of routine intraoperative FFP in cardiac surgery does not lead to increased postoperative blood loss and does not increase postoperative FFP requirements. Despite limitations, the results of FFP trials are congruent, and the available evidence suggests that the prophylactic use of plasma in routine cardiac surgeries is not associated with reduced blood loss or less transfusion requirement, and this practice is not recommended.

SPECIAL REPORT

FACTOR XIII

Class IIb.

1. Use of factor XIII may be considered for clot stabilization after cardiac procedures requiring cardiopulmonary bypass when other routine blood conservation measures prove unsatisfactory in bleeding patients. (Level of evidence C)

Several derivatives of plasma coagulation factor proteases have hemostatic properties and are currently under clinical investigation. Coagulation factor XIII is one such drug that may reduce bleeding and transfusion requirement after cardiovascular operations. Factor XIII is an enzyme that acts upon fibrin, the final component of the common coagulation pathway. Factor XIII is necessary for cross-linking of fibrin monomers to form a stable fibrin clot [106]. The activity of factor XIII in building fibrin polymers is similar to the activity of antifibrinolytic agents. The former builds fibrin cross-links while the latter prevents them from being broken down. It is not known whether factor XIII can be used in conjunction with antifibrinolytic agents or if this combination is safe and effective.

Factor XIII levels are reduced by 30% to 50% in patients who are supported with cardiopulmonary bypass [107–109]. In a randomized study in adult CABG patients given factor XIII at two different doses, there was no difference in bleeding rates compared with controls. However, in this study, increased bleeding occurred in patients with low postoperative plasma levels of factor XIII, irrespective of group assignment [108]. Other types of surgical procedures including neurosurgical, general surgical, and congenital cardiac operations found similar association between decreased factor XIII levels and increased bleeding [110–112]. In a randomized study involving 30 children with congenital cardiac disease, the administration of factor XIII resulted in less myocardial edema, and less total body fluid weight gain [111]. This, along with some basic science research, suggests that factor XIII has antiinflammatory properties. Studies with recombinant fibrinogens identified molecular mechanisms of clot stabilizing effects of factor XIII. Interestingly, thromboelastography identified differences in strength of fibrin cross-linking between the various recombinant forms of fibrin [113, 114].

These findings provided a rationale for the study of factor XIII in patients undergoing cardiovascular procedures. Two small trials of coronary artery bypass patients studied plasma-derived factor XIII concentrates and found reduced postoperative blood loss and transfusion in patients with low preoperative plasma factor XIII levels [108, 109]. Recombinant factor XIII is the subject of a phase II study of patients at moderate risk for hemorrhage after cardiovascular surgery with cardiopulmonary bypass. The phase I trial is complete and provides promising results, but further studies are justified [115]. While the existing literature does not support the routine use of factor XIII at this time, its role as a clot stabilizer is appealing as part of a multimodality treatment in high-risk patients because of its hemostatic properties and low risk of thrombotic complications.

LEUKOREDUCTION

Class IIa.

1. When allogeneic blood transfusion is needed, it is reasonable to use leukoreduced donor blood, if available. Benefits of leukoreduction may be more pronounced in patients undergoing cardiac procedures. (Level of evidence B)

Class III.

1. Currently available leukocyte filters placed on the CPB circuit for leukocyte depletion are not indicated for perioperative blood conservation and may prove harmful by activating leukocytes during CPB. (Level of evidence B)

Adverse effects of transfused blood attributed to the presence of leukocytes in the packed cells include proinflammatory and immunomodulatory effects. In addition, white blood cells can harbor infectious agents (eg, cytomegalovirus). Removing white blood cells from transfused packed red blood cells (leukoreduction or leukodepletion) may reduce the risk of disease transmission and harmful immunomodulation. Indeed, fears over the transmission of prions responsible for variant Creutzfeldt-Jakob disease through transfusion of white blood cell-contaminated red cells triggered the establishment of leukoreduction protocols in the United Kingdom, although later studies demonstrated that red blood cells, platelets, and plasma may also contain prions [116]. Despite this and uncertain literature, leukoreduction filters are used increasingly in various stages of blood processing.

Canada and most European countries perform universal prestorage leukoreduction of donated packed cells. In the United States, most transfused allogeneic blood units are leukoreduced, but local variations exist. Despite widespread use and associated costs, evidence on the effectiveness of universal prestorage leukoreduction of donor blood is equivocal. Reduction of infectious complications and human leukocyte antigen (HLA) immunization are among the most established benefits of leukoreduction, although contradictory results exist in published studies, possibly attributable to the analysis approach (intention-to-treat versus as-treated analysis) [117–124]. Some randomized trials suggest lower mortality with transfusion of prestorage leukoreduced allogeneic blood compared with transfusion of standard buffy-coat-depleted blood in patients having cardiac operations [122–124]. A reanalysis of some of these studies concluded that higher mortality in the nonleukoreduced group and related higher infections are colinear in the patient population, and a cause-effect relationship is uncertain [122]. Regardless of the mechanism, pooled analysis of the data suggests that mortality reduction associated with transfusion of leukoreduced packed cells is greater in patients undergoing cardiac operations compared with other noncardiac operations [124]. Evidence implies that the incidence of posttransfusion purpura and transfusion-associated graft-versus-host disease is lower among patients transfused with leukoreduced blood. Further, leukoreduction is unlikely to eliminate the risk of transfusion-associated graft-versus-host disease in at-risk populations, and other methods (eg, irradiation) are required [125]. More debated potential benefits of leukoreduction include reduced incidence of febrile reactions, minimized multiorgan failure with lung injury, and decreased length of hospital stay [126–135]. Some evidence suggests that the presence of white blood cells in stored blood enhances the deleterious effects of prolonged storage [123].

Given the overall safety of the procedure and the possibility of improving outcomes, the current rising trend in use of leukoreduced donor blood appears to be justified. Concerns with the cost-effectiveness of universal leukoreduction persist [136]. Use of leukoreduced blood likely benefits special groups of patients, especially those patients who receive four or more transfusions [137]. No evidence suggests that use of leukoreduced allogeneic blood reduces transfusion requirements in bleeding patients. Moreover, a large trial demonstrated that leu-

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kodepletion of preoperatively donated autologous whole blood does not improve patient outcomes [138].

Another application of leukocyte filters is in extracorporeal circuit during CPB. During CPB, white blood cells are activated and links exist between activation of white cells and some of the postoperative complications. Leukocytes play an important role in ischemia-reperfusion injury. Therefore, removal of leukocytes from blood at various stages of CPB may reduce inflammatory response and improve organ function. However, the process of in-line leukoreduction during CPB may activate leukocytes even more, and the efficacy of leukocyte removal by the filters is uncertain. Based on available evidence, the previous edition of the STS Blood Conservation Guidelines concluded that none of the putative beneficial effects of leukodepletion during CPB provide tangible clinical benefits, and recommend against its routine use for blood management in CPB [9]. Two recent meta-analyses of rather small and heterogeneous studies published from 1993 to 2005 concluded that leukodepletion during CPB does not reduce 24-hour chest tube drainage or the number of total packed red cell transfusions. Leukodepletion does not attenuate lung injury in patients undergoing CPB (Fig 2) [139, 140].

Limited evidence suggests that in-line leukodepletion during CPB may be beneficial in specific patient populations (eg, patients with left ventricular hypertrophy, prolonged ischemia, chronic obstructive airways disease, pediatric patients undergoing cardiac operations, and patients in shock requiring emergency CABG procedures) [141]. A small trial on patients with renal impairment undergoing on-pump CABG showed that leukodepletion is associated with better renal function [142], and another trial in CABG patients indicated that use of leukofiltration together with polymer-coated circuits is associated with a lower incidence of post-CPB atrial fibrillation in high-risk patients (EuroSCORE [European System for Cardiac Operative Risk Evaluation] of 6 or more) but not in the low-risk patients [143]. Conversely, another trial of CPB leukodepletion in high-risk patients undergoing CABG demonstrated that use of leukocyte filters translates to more pronounced activation of neutrophils, and this intervention did not provide clinical benefits [144].

Although improvements in commercially-available leukocyte filters are likely to occur, the results of more recent studies remain controversial and high quality and consistent evidence to recommend leukocyte filters in routine cardiac operations does not exist [139]. It is likely that specific patient populations benefit to some degree from these devices, but more investigation is needed. Until further studies are available, leukocyte filters attached to the CPB circuit are not indicated because of the lack of clear benefit and the potential for harm.

SPECIAL REPORT

PLATELET PLASMAPHERESIS

Class IIa.

1. Use of intraoperative platelet plasmapheresis is reasonable to assist with blood conservation strategies as part of a multimodality program in high-risk patients if an adequate platelet yield can be reliably obtained. (Level of evidence A)

Platelet plasmapheresis is a continuous centrifugation technique, that when employed using a fast, followed by a slow centrifugation speed, allows for selective removal of a concentrated autologous platelet product from whole blood. During the centrifugation process, the harvested RBCs and platelet-poor plasma are immediately returned to the patient. The concentrated platelet-rich-plasma (PRP) is stored, protected from CPB, and reinfused after completion of CPB. Since platelet dysfunction contributes to CPB-induced bleeding, this strategy of removing platelets from the circulation and "sparing" them from CPB has a theoretical advantage of providing more functional platelets for hemostasis at the end of CPB. Centrifugation at high speeds only produces a platelet-poor plasma product whereas a fast centrifugation followed by a slow centrifugation sequesters more of the platelet fraction and produces PRP [145].

At least 20 controlled trials studied platelet-rich plasmapheresis during cardiac procedures using CPB [145–164]. Most of the controlled trials are prospective and randomized, but with a complex technical procedure such as platelet pheresis, blinding is difficult. Only one study to date "blinded" the platelet pheresis by subjecting control patients to a sham pheresis procedure [160]. The results of that study demonstrated no differences between patients who had PRP harvested and reinfused, and those that did not. Across all studies with regard to hemostasis, the results vary from "no effect" [150, 151, 156, 157, 161] to a significant effect in reducing bleeding and transfusion requirements [149, 153–155, 158, 162–165]. Other studies compared PRP to control groups and demonstrated improved platelet aggregation studies and improved thromboelastographic parameters in the patients who received PRP [145, 159]. Other beneficial effects of PRP harvest and transfusion include an improvement in intrapulmonary shunt fraction and, when PRP harvest is supplemented with platelet gel use, a reduced risk of infection [147, 162, 164, 166]. It seems that an adequate platelet yield obtained from the pheresis procedure is a critical determinant of the efficacy of platelet pheresis in promoting blood conservation. Each study did not specifically report the platelet yield in their PRP product, but in those that did report it, harvest of at least 3×10^{11} platelets, or 28% of the patients circulating platelet volume, is a minimum to achieve a product with optimal hemostasis. Limited value of this procedure accrues to patients taking antiplatelet drugs.

The fact that prophylactic transfusion of platelet concentrates does not improve hemostasis after cardiac operations [167, 168] provides concerns that preoperative harvest of PRP and retransfusion might lack efficacy. The effect of preoperative harvest of fresh whole blood demonstrated a beneficial platelet-protective effect [169, 170]. However, the volume of fresh blood needed to sequester

a large complement of platelets is prohibitively high in most cardiac surgical patients.

The PRP harvest procedure is time- and resource-consuming. Technical errors and possible contamination or wastage of the platelet product are possible and add to the cost and risk of the procedure [171]. Reports of hemodynamic instability during the harvest procedure and during reinfusion of the citrate-containing product exist, but the majority of studies using this technique report no errors or mishaps. It is possible that patients who would benefit most from PRP harvest are the poorest candidates for the procedure, either because of clinical instability or because of low volumes of PRP harvest. Given that PRP harvest is operator dependent, its use as an adjunct to blood conservation strategies for cardiac procedures may be considered if a large yield of platelets is sequestered.

RECOMBINANT ACTIVATED FACTOR VII

Class IIb.

1. Use of recombinant factor VIIa concentrate may be considered for the management of intractable non-surgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB. (Level of evidence B)

Recombinant activated factor VII (r-FVIIa) is used to treat refractory bleeding associated with cardiac operations, although no large randomized trial data exists to support this use. A recent randomized controlled trial of r-FVIIa of 172 patients with bleeding after cardiac surgery reported a significant decrease in reoperation and allogeneic blood products, but a higher incidence of critical serious adverse events, including stroke, with r-FVIIa treatment [172]. Multiple case reports, meta-analyses, registry reviews, and observational studies appear in the published literature in hopes of providing clarity to the indications for use and associated side-effects [173–178]. No clear cut consensus results from these reviews. There is little doubt that r-FVIIa is associated with reduction in bleeding and transfusion in some patients. However, which patients are appropriate candidates for r-FVIIa are uncertain and neither the appropriate dose nor the thrombotic risks of this agent are totally clear. Despite multiple new reports, we did not find convincing evidence to support a change to our original recommendation in previously published guidelines.

ANTITHROMBIN III

Class I.

1. Antithrombin III (AT) concentrates are indicated to reduce plasma transfusion in patients with AT-mediated heparin resistance immediately before cardiopulmonary bypass. (Level of evidence A)

Class IIb.

1. Administration of AT concentrates is less well established as part of a multidisciplinary blood management protocol in high-risk patients who may have AT depletion or in some, but not all, patients who are unwilling to accept blood products for religious reasons. (Level of evidence C)

Plasma-derived or recombinant antithrombin III (AT) concentrates are approved for use in patients with hereditary AT deficiency to prevent perioperative thrombotic complications. These agents are used off-label to either manage AT mediated heparin resistance or to prevent perioperative thrombotic complications and target organ injury in patients with acquired AT deficiency.

Heparin is by far the most commonly used anticoagulant for the conduct of CPB. Heparin binds to the serine protease inhibitor AT causing a conformational change that results in dramatic change in affinity of AT for thrombin and other coagulation factors. After binding to its targets, the activated AT inactivates thrombin and other proteases involved in blood clotting, including factor Xa. Heparin's anticoagulant effect correlates well with plasma AT activity. Impaired heparin responsiveness or heparin resistance is often attributed to AT deficiency [179]. Antithrombin activity levels as low as 40% to 50% of normal, similar to those observed in patients with heterozygotic hereditary deficiency [180], are commonly seen during and immediately after CPB [181, 182]. Acquired perioperative reductions in plasma AT concentrations are related to a time-dependent drop associated with preoperative heparin use (ie, approximately 5% to 7% decrease in AT levels per preoperative day of heparin), hemodilution, or consumption during CPB [183, 184].

Heparin resistance is defined as the failure to achieve activated clotting time of at least 400 s to 480 s after a standard heparin dose, although there is a substantial variability in the definition of the "standard" heparin dose, ranging from less than 400 to 1,200 U/kg [185]. Plasma proteins and the formed elements of blood modify the anticoagulant effect of heparin [186, 187]. As a result, the most common cause of heparin resistance in patients not receiving preoperative heparin is likely due to inactivation of heparin by bound proteins or other blood elements [188–192].

A minority of patients undergoing CPB are resistant to heparin. Antithrombin depletion causes heparin resistance in some of these patients receiving preoperative heparin [193–195]. Empiric treatment for this type of heparin resistance often involves administration of either FFP, plasma-derived AT, or recombinant human AT. Twelve of 13 previous reports indicate that AT supplementation by either FFP [196, 197] recombinant AT [8, 198, 199], or plasma-derived AT concentrates [198, 200–206] effectively manage heparin resistance. The use of factor concentrates or recombinant AT offers unique advantages because of reduced blood-borne disease transmission and reduced incidence of fluid overload compared with FFP. Two recent randomized, controlled studies demonstrated that recombinant AT treats heparin resistance [8, 199]. These two studies demonstrated that recombinant human AT effectively restores heparin responsiveness before CPB in the majority of patients with heparin resistance [8, 199]. The primary endpoint of these trials was the proportion of patients requiring

administration of 2 units FFP to achieve therapeutic anticoagulation. A significantly ($p < 0.001$) lower percentage of patients required FFP in the recombinant human AT-treated group (20%) compared with the placebo group (86%). Although these studies achieved the primary endpoint of reduced FFP transfusion, they did not assess the effect of AT concentrates on suppression of the hemostatic system activation during and after CPB.

In addition to the management of prebypass heparin resistance, restoration of AT levels during CPB may limit inflammatory activation and replace AT depleted by inadequate heparinization during CPB. During CPB, blood interfaces with the artificial surface of the bypass circuit which generates a powerful stimulus for thrombin generation that is not completely suppressed by heparin. In addition, subtherapeutic anticoagulation can result in excessive hemostatic system activation leading to generation of thrombin and plasmin, which then can result in depletion of clotting factors and platelets (a disseminated intravascular coagulationlike consumptive state). The AT-mediated heparin resistance may be an early warning sign of inadequate anticoagulation during CPB, leading to an increase in bleeding and/or thrombotic complications.

Previous studies suggest that AT supplementation attenuates thrombin production and fibrinolytic activity during CPB [184, 198]. This suppression of thrombin production and fibrinolytic activity during CPB may represent better inhibition of hemostatic activation than that achieved with heparin but without AT supplementation [198]. Other studies show an inverse relationship between plasma AT concentration and markers of both thrombin activation (eg, fibrinopeptide A, fibrin monomer) and fibrinolytic activation (D-dimer) [184, 207]. Preservation of the hemostatic system by AT supplementation may reduce bleeding and provide a better hemostatic profile after CPB. In general, less bleeding and blood transfusion occur in patients whose hemostatic system is better preserved after the physiologic stresses of CPB [208–211].

Thromboembolic complications early after cardiac operations are potentially lethal. Antithrombin is a major in vivo inhibitor of thrombin, and a deficiency of AT in the presence of excess thrombin after CPB provides a potent prothrombotic environment that may cause thromboembolic complications. This concept is supported by case reports describing catastrophic thrombosis in a few patients with low AT III levels in the perioperative period [212, 213]. Additionally, observational studies suggest an indirect relationship between AT levels and perioperative complications [214–216]. Ranucci and coworkers [216] showed that patients who suffered adverse neurologic outcomes, thromboembolic events, surgical reexploration for bleeding, or prolonged intensive care unit (ICU) stay after cardiac operations had reduced AT III levels on admission to the ICU compared with patients without complications [216]. Two other observational studies confirm an inverse relationship between AT III activity and adverse thromboembolic patient outcomes [214, 215]. Thrombotic complications involving target organ injury may be under reported after cardiac procedures, especially in high-risk patients [217]. This target organ injury may be related to microvascular thrombosis from a procoagulant postoperative environment, at least in part due to AT deficiency. Based on these published reports, it may be reasonable to add AT, preferably in concentrated form, in patients at increased risk for end-organ thrombotic complications after CPB.

FACTOR IX CONCENTRATES, PROTHROMBIN COMPLEX CONCENTRATES, AND FACTOR VIII INHIBITOR BYPASSING ACTIVITY

Class IIb.

1. Use of factor IX concentrates, or combinations of clotting factor complexes that include factor IX, may be considered in patients with hemophilia B or who refuse primary blood component transfusion for religious reasons (eg, Jehovah's Witness) and who require cardiac operations. (Level of evidence C)

An intermediate step in clot formation involves activation of factor IX by the tissue factor/factor VIIa complex [218]. In some patients requiring cardiac procedures, factor IX concentrates are used for one of four purposes: (1) control of perioperative bleeding in patients with hemophilia B [219–221]; (2) prophylaxis in high-risk patients unable to accept primary component transfusions for religious reasons (eg, Jehovah's Witness) [222]; (3) as part of prothrombin complex concentrate (Beriplex) for reversal of warfarin before operative intervention; and (4) part of the factor VIII inhibitor bypassing activity in patients with factor VIII inhibitors requiring operative intervention [92, 223, 224]. Of these options, use of factor IX concentrates is most reasonable for Jehovah's Witness patients [222].

Jehovah's Witness patients refuse transfusion on religious grounds. Blood products encompassed with this refusal are defined by each individual Jehovah's Witness patient confronted with a need for cardiac procedure. Typically primary components include packed red blood cells, platelets, and fresh frozen plasma. Changes in the Jehovah's Witness blood refusal policy now give members the personal choice to accept certain processed fractions of blood, such as factor concentrates and cryoprecipitate [225, 226]. In Jehovah's Witness patients, a multimodality approach to blood conservation is reasonable [227], and addition of factor concentrates augments multiple other interventions. Fractionated factor concentrates, like factor IX concentrates or one of its various forms (Beriplex or factor VIII inhibitor bypassing activity), are considered "secondary components" and may be acceptable to some Jehovah's Witness patients [222]. Addition of factor IX concentrates may be most useful in the highest risk Jehovah's Witness patients.

d) Blood Salvage Interventions

EXPANDED USE OF RED CELL SALVAGE USING CENTRIFUGATION

Class IIb.

1. In high-risk patients with known malignancy who require CPB, blood salvage using centrifugation of blood salvaged from the operative field may be considered since substantial data support benefit in patients without malignancy, and new evidence

SPECIAL REPORT

suggests worsened outcome when allogeneic transfusion is required in patients with malignancy. (Level of evidence B)

In 1986, the American Medical Association Council on Scientific Affairs issued a statement regarding the safety of blood salvage during cancer surgery [228]. At that time, they advised against its use. Since then, 10 observational studies that included 476 patients who received blood salvage during resection of multiple different tumor types involving the liver [229–231], prostate [232–234], uterus [235, 236], and urologic system [237, 238] support the use of salvage of red cells using centrifugation in cancer patients. In seven studies, a control group received no transfusion, allogeneic transfusion, or preoperative autologous donation. In all studies, the centrifugation salvage group received less allogeneic blood and had equivalent long-term outcomes compared with control patients. None of the studies found evidence of subsequent wide-spread metastasis from salvaged red cells harvested using centrifugation in operations for malignancy.

Because operations involving tumor removal may have less allogeneic blood transfusion with blood salvage, the theoretical risk of avoiding blood salvage needs to be examined more closely. First, there are numerous reports suggesting that the presence of circulating tumor has no prognostic significance, and one author suggested that outcome was better in patients with higher circulating tumor cells [239, 240]. Second, multiple reports indicate that allogeneic transfusion increases the rates of recurrence after tumor operations. Two recent meta-analyses of these reports suggest that patients suffer nearly a twofold increase in recurrence when exposed to allogeneic transfusion [241, 242].

There are numerous reports of leukocyte depletion filters or radiation being used to eliminate malignant cells from salvaged blood [243–245]. These studies suggest that a 3-log to 4-log reduction in tumor burden is achieved with leukocyte depletion filters whereas a 12-log reduction is achieved with radiation [246]. While debate exists among advocates of either removal technique as to the best strategy, in six of the seven studies referenced above where control groups existed, neither technique was used. In the seventh manuscript, a leukodepletion filter was used. The bulk of evidence suggests that the addition of tumor cells into circulation from salvaged red cells is of little prognostic significance.

No data exist to contradict the use of blood salvage in malignant surgery and substantial data exist to support worsened outcome when the alternative therapy (allogeneic transfusion) is used. The use of centrifugation of salvaged blood in patients with malignancy who require cardiac procedures using CPB is less well established but may be considered.

PUMP SALVAGE

Class IIa.

1. Consensus suggests that some form of pump salvage and reinfusion of residual pump blood at the end of CPB is reasonable as part of a blood management program to minimize blood transfusion. (Level of evidence C)
2. Centrifugation instead of direct infusion of residual pump blood is reasonable for minimizing post-CPB allogeneic RBC transfusion. (Level of evidence A)

Most surgical teams reinfuse blood from the extracorporeal circuit (ECC) back into patients at the end of CPB as part of a blood conservation strategy. Currently, two blood salvaging techniques exist: (1) direct infusion of post-CPB circuit blood with no processing; and (2) processing of the circuit blood, either by centrifugation of by ultrafiltration, to remove either plasma components or water soluble components from blood before reinfusion. Centrifugation of residual CPB blood produces concentrated red cells mostly devoid of plasma proteins, whereas ultrafiltration produces protein-rich concentrated whole blood [247].

Two studies compared the clinical effects of direct infusion, centrifugation and ultrafiltration. Sutton and colleagues [248] randomly allocated 60 patients undergoing elective CABG using CPB [248]. They observed significantly longer partial thromboplastin times in the centrifugation group compared with the direct infusion and ultrafiltration groups 20 minutes after circuit blood administration. Importantly, there were no differences in blood product usage, total chest tube drainage, or discharge hematocrit values. Eichert and coworkers [249] prospectively randomized 60 patients undergoing elective CABG operations into three blood salvage interventions (described above). Among the three groups, there were no significant differences in postoperative hemoglobin levels, postoperative chest tube drainage, platelet counts, or partial thromboplastin times at 12 hours after operation. Allogeneic blood transfusion rates were not reported.

Two studies compared the effectiveness of centrifugation compared with ultrafiltration in concentrating post-CPB ECC blood to minimize blood loss and transfusion requirements. Boldt and coworkers [247] studied 40 nonrandomized patients undergoing elective CABG procedures and discovered no significant difference in blood loss or frequency of donor blood transfusion between the centrifugation and ultrafiltration groups. Samolyk and coworkers [250] used a case-matched control study to compare centrifugation and ultrafiltration in 100 patients; there was no difference in blood utilization or postoperative bleeding between groups.

A number of studies compared the effects of direct infusion of unprocessed post-CPB blood versus centrifugation. In a prospective randomized study of 40 elective patients having cardiac procedures, Daane and coworkers [251] found significantly less allogeneic red cell use in the centrifugation group (2.4 ± 1.3 units of PRBC) versus the direct infusion group (3.2 ± 1.1 units PRBC; $p = 0.046$). Fresh frozen plasma and platelet administration were not significantly different between the two groups. Walpoth and associates [252] randomly assigned 20 patients undergoing elective CABG procedures to either

direct infusion or centrifugation. There was no significant difference in postoperative day 1 hemoglobin values or allogeneic blood transfusions between the two groups. Wiefferink and associates [253] randomized 30 primary elective CABG surgery patients and found elevated D-dimer levels (suggesting increased intravascular fibrin degradation) in the early postoperative period in the direct infusion group compared with the centrifugation group. Chest tube drainage and transfusion requirements were also higher in the direct infusion group. In this study, direct infusion of mediastinal blood by an autotransfusion system in only the centrifugation group undoubtedly impacted transfusion requirements. These findings support earlier results of Moran and colleagues [254] who studied the safety and effectiveness of centrifugation of residual CPB blood among patients undergoing cardiopulmonary bypass (including CABG and valve procedures). For 50 randomized patients, they reported significantly ($p < 0.05$) less allogeneic RBC exposure in the centrifugation group (1,642 ± 195 mL) compared with the direct infusion group (2,175 ± 175 mL).

Two limitations to the current body of literature on the topic of salvaging post-CPB ECC blood are noteworthy: (1) most of the current literature focuses on elective CABG patients; and (2) many studies include small sample sizes. From the available literature, no firm distinction among these techniques for salvaging post-CPB ECC blood arises. Additional studies are required to clarify the effectiveness and efficacy of these approaches to pump salvage. However, consensus supports the practice of pump salvage compared with no salvage of residual blood.

e) Minimally Invasive Procedures

AORTIC ENDOGRAFTS

Class I.

1. Thoracic endovascular aortic repair (TEVAR) of descending aortic pathology reduces bleeding and blood transfusion compared with open procedures and is indicated in selected patients. (Level of evidence B)

Reports of thoracic endovascular aortic repair (TEVAR) for descending thoracic aortic pathology appeared in the literature more than 15 years ago [255]. Since then, surgeons embraced TEVAR without evidence from randomized comparisons of open repair versus TEVAR. The uptake of TEVAR outstripped adequate evaluation largely because of perceived benefit in morbidity, and possibly mortality, associated with TEVAR. Recently, two meta-analyses of published nonrandomized comparisons of TEVAR to open repair appeared in the literature [256, 257]. The most recent of these meta-analyses encompassed 45 nonrandomized studies involving more than 5,000 patients [256]. The results suggest that TEVAR may reduce early death, paraplegia, renal insufficiency, transfusions, reoperation for bleeding, cardiac complications, pneumonia, and length of stay compared with open surgery. Anecdotal evidence suggests that this benefit extends to Jehovah's Witness patients [258, 259]. The early adoption of TEVAR seems justified based on these less than rigorous studies. If these results are confirmed in randomized trials, TEVAR represents a paradigm shift in the treatment of thoracic aortic disease, and this shift may have already occurred.

OFF-PUMP PROCEDURES

Class IIa.

1. Off-pump operative coronary revascularization (OPCABG) is a reasonable means of blood conservation, provided that emergent conversion to on-pump CABG is unlikely and the increased risk of graft closure is considered in weighing risks and benefits. (Level of evidence A)

In the original publication of the STS Blood Conservation Guidelines, patients having OPCABG had reduced blood utilization and postoperative bleeding [9]. Since publication of this practice guideline, new information suggests that blood transfusion and significant postoperative bleeding is less common among patients treated with OPCABG compared with conventional CABG using CPB [260–262]. These findings support our initial recommendation for the use of OPCABG as a blood conservation intervention, especially in skilled hands where conversion to an open CABG using CPB is unlikely [263]. However, several threads of evidence, including a large multiinstitution comparison, suggest that graft patency is reduced in OPCABG patients [11, 264].

f) Perfusion Interventions

MICROPLEGIA

Class IIb.

1. Routine use of a microplegia technique may be considered to minimize the volume of crystalloid cardioplegia administered as part of a multimodality blood conservation program, especially in fluid overload conditions like congestive heart failure. However, compared with 4:1 conventional blood cardioplegia, microplegia does not significantly impact RBC exposure. (Level of evidence B)

Blood cardioplegia is the most common form of myocardial preservation during cardiac surgery with the crystalloid component facilitating cardiac arrest and providing myocardial protection during ischemia and reperfusion [265]. Microplegia is a term used to describe the mixing of blood from the CPB circuit with small quantities of concentrated cardioplegia additives [266]. This technique relies on precision pumps to deliver small and accurate quantities of concentrated cardioplegia additives. The concentrated additives offer the theoretical advantage of minimizing fluid overload and hemodilutional anemia.

Four studies suggest that microplegia results in less hemodilution compared with traditional 4:1 blood to crystalloid cardioplegia systems [267–270]. These studies showed an 11-fold to 27-fold increase in delivered cardioplegia volume in the 4:1 blood cardioplegia groups, but

similar allogeneic blood product usage compared with the microplegia groups. In each of these studies, the clinical outcomes were not statistically different between groups, although a potential type II error exists because of the low event rates for adverse sequelae and the small sample sizes.

Minimizing the crystalloid component of blood cardioplegia is intuitively advantageous with respect to minimizing hemodilutional anemia and possible subsequent allogeneic RBC transfusion. The peer-reviewed medical literature focuses on cardioplegia volume delivered to patients and not on blood conservation. More data are required to assess whether microplegia has an appreciable effect on transfusion rates and blood conservation, but microplegia use may be considered as part of a multimodality blood management program.

BLOOD CONSERVATION IN ECMO AND SHORT-TERM VENTRICULAR SUPPORT

Class I.

1. Extracorporeal membrane oxygenation patients with heparin-induced thrombocytopenia should be anticoagulated using alternate nonheparin anticoagulant therapies such as danaparoid or direct thrombin inhibitors (eg, lepirudin, bivalirudin, or argatroban). (Level of evidence C)

Class IIa.

1. It is reasonable to consider therapy with a lysine analog antifibrinolytic agents (epsilon aminocaproic acid, tranexamic acid) to reduce the incidence of hemorrhagic complications in ECMO patients. (Level of evidence B)

Class IIb.

1. It may be helpful to use recombinant activated factor VII as therapy for life-threatening bleeding in ECMO patients. The potential benefit of this agent must be weighed against numerous reports of catastrophic acute thrombotic complications. (Level of evidence C)

Over the last decade patients who require cardiac operations are sicker and have more comorbidities and less functional reserve. The increased acuity of patients presenting for cardiac operations results in more frequent use of prolonged circulatory support. Extracorporeal membrane oxygenation and short-term ventricular support devices can cause additional serious clinical sequellae that often translates into excess bleeding and blood transfusion [271, 272]. Hemolysis of red cells leading to transfusion presents a special problem in patients supported with these devices [273].

Extracorporeal membrane oxygenation is used to provide temporary (days to weeks) respiratory (venovenous) or cardiorespiratory (venoarterial) support, to critically ill adult, pediatric, and neonatal patients failing conventional therapy because of cardiopulmonary failure. Venovenous ECMO is most frequently used for pulmonary disorders such as adult respiratory distress syndrome, congenital diaphragmatic hernia, and meconium aspiration, whereas venoarterial ECMO is indicated for reversible cardiogenic shock, or as a bridge to more permanent ventricular assist device insertion or heart transplantation. The Extracorporeal Life Support Organization developed guidelines for the practice of ECMO [274].

Thrombotic and bleeding complications are common with ECMO. In a recent review of 297 adult ECMO patients, 11% had serious neurologic events related to intracranial infarct or hemorrhage and19% had clots in the ECMO circuit, and other complications included cardiac tamponade (10%) and serious bleeding from cannula insertion sites (21%), surgical incisions (24%), and the gastrointestinal tract (4%) [275]. Other reports indicate that intracranial hemorrhage is particularly common in ECMO patients with renal dysfunction or thrombocytopenia [276]. Reports document ECMO-related coagulopathy due to platelet dysfunction and hemodilution with consumptive factor depletion [277, 278]. Although the challenge of balancing the need for sufficient anticoagulation to prevent ECMO circuit thrombosis while minimizing bleeding risk exists, there are few objective data to guide ECMO anticoagulation therapy.

Consensus ECMO guidelines advocate heparin anticoagulation to achieve a target activated clotting test time between 160 s and 240 s [107, 274, 279, 280]. However, recent studies question the activated clotting time as a reliable indicator of heparin effect with ECMO [281], and correlate increased heparin dosing with improved survival [282]. Nonrandomized observational ECMO studies employing modified heparin protocols report reduced thrombohemorrhagic complications [283, 284]. Similarly, many small nonrandomized studies evaluating heparin-coated ECMO systems with or without heparin administration describe reduced blood loss, but also thrombotic complications [285–287]. Other proposed alterations to ECMO guidelines include alternate heparin monitoring tests (eg, activated partial thromboplastin time, anti-Xa, thromboelastography, heparin/protamine titration, and direct heparin level measurements) [282].

Prolonged ECMO or ventricular support using heparin anticoagulation can cause heparin-induced thrombocytopenia. In this setting, anticoagulation regimens including danaparoid [288] and direct thrombin inhibitors such as lepirudin, bivalirudin, or argatroban [289–291] are useful alternatives.

Several studies advocate the use of antifibrinolytic agents in ECMO patients to limit bleeding complications and blood transfusion. One study reports a potentially blood sparing effect of aprotinin in ECMO patients but this is unlikely to be useful given the risk/benefit analysis described above [292]. Retrospective evaluations of use of epsilon aminocaproic or tranexamic acid therapy in post-cardiotomy ECMO patients suggest reduced bleeding complications [293–295]. A randomized study of hemorrhagic complications in 29 neonates could not reproduce these findings [296]. A randomized study of 60 patients evaluating leukoreduction using a Pall LG6 leukocyte filter during extracorporeal circulation also found no reduction in bleeding complications or transfusion [297].

Consensus guidelines for blood component therapy in ECMO patients advocates transfusion to assure adequate oxygen carrying capacity, normal AT III activity (80% to 120% of control) and fibrinogen levels (250 to 300 mg/dL), while maintaining a platelet count greater than 80,000 to 100,000/μL with platelet transfusion [274, 279, 280]. Notably, although the generalized effects of ECMO on coagulation, fibrinolysis, and platelet function are well documented [278], studies in neonates often focus on platelet number and function. To maintain target platelet counts, transfusion requirements tend to be higher in neonates with meconium aspiration or sepsis, and in those receiving venoarterial compared with venovenous ECMO [298]. Although some studies advocate prophylactic transfusion to target platelet counts that are higher than standard guidelines [299], there is concern that prophylactic rather than therapeutic platelet transfusion results in excessive platelet transfusion in ECMO patients with concomitant detrimental effects [300].

Bleeding is a common complication in ECMO patients. Likely causes of bleeding include overanticoagulation and decreased platelet number and function. Significant bleeding occurs from minimal interventions such as tracheal suction or nasogastric tube placement, or from minor surgical interventions [301]. Some reports of refractory bleeding with ECMO describe benefit from r-FVIIa therapy [302–304]. Unfortunately, other reports describe catastrophic acute thrombotic complications with this agent, suggesting this therapy should be considered as a last resort [305, 306].

MINICIRCUITS AND VACUUM-ASSISTED VENOUS DRAINAGE

Class I.

1. Minicircuits (reduced priming volume in the minimized CPB circuit) reduce hemodilution and are indicated for blood conservation, especially in patients at high risk for adverse effects of hemodilution (eg, pediatric patients and Jehovah's Witness patients). (Level of evidence A)

Class IIb.

1. Vacuum-assisted venous drainage in conjunction with minicircuits may prove useful in limiting bleeding and blood transfusion as part of a multimodality blood conservation program. (Level of evidence C)

Abundant evidence suggests that preoperative anemia or small body size is a risk for postoperative blood transfusion [9], but it seems likely that these patients with reduced red cell volume (either from anemia or from small body size) risk severe hemodilution with conventional CPB as a cause of blood transfusion [307]. Reduced priming volume in the CPB circuit (minicircuits) appeals to surgeons for many reasons. Paramount among these is the potential for reduced hemodilution and blood utilization. Minicircuits have particular appeal to pediatric cardiac surgeons since the effects of hemodilution in conventional CPB circuits are greatest in small patients. Acceptance of minicircuits is not universal, partly because most minicircuit perfusion configurations require a closed venous reservoir or no venous reservoir [308]. Introduction of air into the closed venous system risks an "air-lock" in the CPB circuit, and absence of a venous reservoir risks exsanguination from uncontrolled bleeding in the operative field. Experience with minicircuits includes use in conjunction with beating heart procedures [309], in usual cardiac procedures [310–314] and in Jehovah's Witness patients [315, 316].

Nine of 14 randomized trials [309, 310, 317–327] and a well-constructed meta-analysis [328] suggest benefit from minicircuits with reduced transfusion and postoperative bleeding. There is near universal agreement that minicircuits limit markers of inflammation compared with conventional CPB circuits [312, 313, 329]. Summation of available evidence suggests that minicircuits provide a valuable alternative that limits hemodilution and blood usage after cardiac procedures.

Many reports of use of minicircuits for extracorporeal circulation use vacuum-assisted venous drainage (VAVD). A VAVD in conjunction with minicircuits may improve hemostasis, limit chest tube drainage, and decrease blood transfusion, compared with CPB circuits with gravity venous drainage [330–333]. The majority of air microemboli originate in the venous line of the CPB circuit [334]. Most [335–337], but not all studies [338] suggest that VAVD entrains air and leads to increased systemic microemboli compared with gravity venous drainage [335–341]. The effect of microemboli can be minimized by flooding the operative field with carbon dioxide and adjustment of perfusion parameters [336, 339, 341, 342]. A VAVD may [343] or may not [344, 345] cause hemolysis within the CPB circuit. Given the potential limitations of VAVD, use of this technology necessitates caution and adjustment of perfusion techniques [336, 339, 342], but may provide benefit, especially in pediatric patients [332].

BIOCOMPATIBLE CPB CIRCUITS

Class IIb.

1. Use of biocompatible CPB circuits may be considered as part of a multimodality program for blood conservation. (Level of evidence A)

Biocompatible surfaces for CPB circuits are commercially available. More than 200 publications address the potential benefit of these circuits. A recent meta-analysis reviewed bleeding outcomes associated with these biocompatible surfaces [346]. In this review, Ranucci and coworkers [346] identified a cohort of 128 publications that explored outcomes in patients treated with these circuits. From these 128 articles, 36 randomized clinical trials contained information on more than 4,000 patients. In the preliminary analysis, the authors found less bleeding and blood transfusion in patients treated with biocompatible circuits. However, in a subgroup of 20 of the highest quality randomized clinical trials, benefits related to blood conservation

disappeared. The authors of this well-done meta-analysis suggest that use of biocompatible surfaces without other measures of blood conservation results in limited clinical benefit [346]. Use of biocompatible CPB circuits as part of a multimodality program in conjunction with closed CPB circuits, separation of cardiotomy suction, minicircuits to reduce priming volume may be useful for blood conservation.

ULTRAFILTRATION

Class I.

1. Use of modified ultrafiltration (MUF) is indicated for blood conservation and reducing postoperative blood loss in adult cardiac operations using CPB. (Level of evidence A)

Class IIb.

1. Benefit of the use of conventional or zero balance ultrafiltration (ZBUF) is not well established for blood conservation and reducing postoperative blood loss in adult cardiac operations. (Level of evidence A)

Ultrafiltration is an option to limit hemodilution secondary to CPB. Ultrafiltration devices can be integrated in parallel into existing CPB circuits for this purpose. Ultrafiltration filters water and low-molecular weight substances from the CPB circuit, producing protein-rich concentrated whole blood that can be returned to the patient. In cardiac surgery, three variants are utilized: (1) conventional ultrafiltration run during CPB but not after; (2) modified ultrafiltration (MUF) run after completion of CPB using existing cannulae; and (3) zero balance ultrafiltration (ZBUF) similar to conventional ultrafiltration but with replacement of lost volume with crystalloid solution. A number of investigations, including a meta-analysis of 10 randomized trials [347], focused on use of these methods during and after CPB.

Conventional Ultrafiltration. Conventional ultrafiltration is a method of ultrafiltration used during CPB. One meta-analysis [347], four randomized trials [348–351], and two cohort studies [352, 353] report the use of conventional ultrafiltration in patients undergoing cardiac procedures using CPB. Subgroup analysis of five studies included in the meta-analysis by Boodhwani [347] demonstrated no advantage in terms of red cell usage or blood loss with conventional ultrafiltration alone [349–353].

Modified Ultrafiltration. Modified ultrafiltration is a method of ultrafiltration used after the cessation of CPB. Subgroup analysis in the meta-analysis of Boodhwani [347], involving more than 1,000 patients, found significantly reduced bleeding and blood product usage with MUF. A recent study by Zahoor and colleagues [354], who randomized 100 patients undergoing CABG or valve surgery, found a significant reduction in blood loss at 24 hours ($p < 0.001$), and less requirement for PRBC ($p < 0.001$), FFP ($p = 0.0012$), and platelet ($p < 0.001$) transfusions in the MUF-treated group. Luciani and colleagues [355] (reported in the meta-analysis by Boodhwani) found significant reduction transfusion in a randomized group of 573 patients undergoing all types of cardiac surgery who received MUF compared with control patients who did not have ultrafiltration [355]. These results suggest benefit from MUF in reducing hemodilution and limiting blood transfusion.

Zero Balance Ultrafiltration. With ZBUF, the ultrafiltrate fluid is replaced with an equal volume of balanced electrolyte solution during CPB. Patients may benefit from ZBUF through the removal of mediators and products of systemic inflammatory response syndrome, rather than as a result of fluid removal [356]. Randomized controlled trials investigating ZBUF in adult cardiac procedures did not demonstrate a reduction in blood loss or transfusion with the application of ZBUF [357, 358].

g) Topical Hemostatic Agents

HEMOSTATIC AGENTS PROVIDING ANASTOMOTIC SEALING OR COMPRESSION

Class IIb.

1. 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 multimodality blood management program. (Level of evidence C)

In recent years, the increasing complexity of cardiac procedures led to the introduction of a number of topical hemostatic agents intended to reduce or eliminate bleeding from graft-vessel or from graft-cardiac anastomoses. Multiple topical agents are commercially available and some evidence suggests varying amounts of benefit from these agents (Table 3). Two types of topical hemostatic agents are used at anastomotic sites: (1) compression hemostatic agents, and (2) anastomotic sealants.

Compression hemostatic agents are the most commonly used adjuncts for anastomotic site hemostasis. These agents provide a scaffold for clot formation. They provide wound compression as a result of swelling associated with clot formation. The two most commonly used agents are oxidized regenerated cellulose and microfibrillar collagen. Oxidized regenerated cellulose which is known by the brand names Surgicel or Oxycel is a bioabsorbable gauze available in the form of woven sheets of fibers. How oxidized cellulose accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. This agent can be left in the wound and will be completely resorbed by 6 to 8 weeks. Oxidized regenerated cellulose is bacteriostatic with broad spectrum antimicrobial activity including activity against methicillin-resistant *Staphylococcus aureus* [359]. These agents proved effective for suture line bleeding in nonrandomized trials, and gained wide spread acceptance without much evidence base to support their use. They depend on a normal clotting system and are less effective in patients with coagulopathy.

Microfibrillar collagen (Avitene, Colgel, or Helitene) is a water-insoluble salt of bovine collagen that adheres to

Table 3. Topical Hemostatic Agents Used in Cardiac Operations for Local Control of Bleeding

Agent	Commercial Name	Composition	Mechanism of Action	Class of Recommendation
Oxidized regenerated cellulose for wound compression	Surgicel and Oxycel	Oxidized cellulose	Accelerate clotting by platelet activation followed by swelling and wound compression. Some bacteriostatic properties.	Class IIb
Microfibrillar collagen	Avitene, Colgel, or Helitene	Bovine collagen shredded into fibrils	Collagen activates platelets causing aggregation, clot formation, and wound sealing.	Class IIb
Combined compression and sealant topical agent	Recothrom or Thrombin JMI added to USP porcine Gelfoam, Costasis, or FloSeal	Bovine fibrillar collagen or bovine gelatin combined with thrombin and mixed with autologous plasma	Activation of platelet-related clotting followed by swelling and wound compression. Recombinant thrombin has potential safety advantage. Combination of compression and sealant agents.	Class IIb
Fibrin sealants ("fibrin glue")	Tisseel, Beriplast, Hemaseel, Crosseal	Source of fibrinogen and thrombin mixed with antifibrinolytics combined at anastomotic sites	Fibrin matrix serves to seal the wound. Contains either aprotinin or tranexamic acid.	Class IIb
Synthetic cyanoacrylate polymers	Omnex	Polymers of two forms of cyanoacrylate monomers	Seals wounds without need for intact clotting mechanism.	Class IIb
Synthetic polymers of polyethylene glycol	CoSeal and DuraSeal	Polymers of polyethylene glycol cross link with local proteins	Polymers and proteins form matrix sealant.	Class IIb
Sealant mixture of bovine albumin and glutaraldehyde	BioGlue	Albumin and glutaraldehyde dispensed in 2-syringe system	Sealant created without need for intrinsic clotting system by denaturation of albumin. Safety concerns because of glutaraldehyde toxicity.	Class IIb
Large surface area polysaccharide hemospheres	Arista, HemoStase	Plant-based polysaccharides with a very large surface area	Rapidly dehydrate blood by concentrating serum proteins, platelets, and other blood elements on the surface of contact.	Class IIb
Chitin-based sealants	Celox, HemCon, Chitoseal	Naturally occurring polysaccharide polymer	Chitin forms clots in defibrinated or heparinized blood by a direct reaction with the cell membranes of erythrocytes. Probably induces local growth factors.	Class IIb
Antifibrinolytic agents in solution	Trasylol or tranexamic acid	Antifibrinolytic agents dissolved in saline	Limit wound-related generation of plasmin.	Class IIa

anastomotic bleeding sites and provides some hemostatic effect by initiation of platelet activation and aggregation. A single nonrandomized trial suggests that microfibrillar collagen reduces postoperative chest tube drainage compared with oxidized regenerated cellulose [360]. These compounds have no known bacteriostatic properties. Microfibrillar collagen can cause end-organ damage if blood containing this material is returned to the circulation through pump suction or cell salvage devices [361].

Multiple forms of commercially available anastomotic sealants exist. Sealants attempt to create an air-tight seal at anastomotic sites to prevent localized bleeding. Many anastomotic sealants use some form of thrombin to cleave fibrinogen and form a clot to seal the anastomotic site. In the past, bovine plasma served as the most common source of thrombin. Purified bovine thrombin (Thrombin JMI) generates antibodies when infused into humans much as any foreign protein would do [362]. In 2008, the FDA approved recombinant human thrombin (Recothrom). This compound provides an additional potential safety benefit compared with bovine thrombin because of the generation of fewer antibodies compared with the bovine product [362, 363]. A single randomized trial suggests that Recothrom has equivalent hemostatic efficacy compared with bovine thrombin but with significantly less antibody production [363].

One anastomotic sealant is a combination of bovine-derived gelatin and human-derived thrombin. It is known as FloSeal and, upon contact with blood proteins, the gelatin-based matrix swells while high thrombin levels hasten clot formation with a combination of pressure and enhanced clotting to seal bleeding sites. The thrombin in this product is manufactured by heating human thrombin to reduce viral load although it is not effective in totally eliminating the risk of infection. Two randomized studies suggest improved anastomotic hemostasis and reduced blood transfusion with FloSeal compared with compression alone when applied to actively bleeding sites in patients with difficult-to-control bleeding [364, 365]. In one of these studies, a significant number of patients developed antibodies to both bovine thrombin and other bovine clotting factors, raising concerns about delayed coagulopathy and potential safety risk with repeat exposure [364].

One topical sealant that is commercially available under the trade name of Costasis, is a composite of bovine microfibrillar collagen and bovine thrombin mixed with autologous plasma obtained at the time of operation. This mixture is delivered as a spray onto the bleeding site. One randomized controlled study suggests that Costasis is superior to microfibrillar collagen alone for multiple surgical indications [366].

Tissue sealants containing fibrinogen are used for hemostasis at anastomotic sites. These compounds have a variety of trade names (Tisseel, Beriplast, Hemaseel, Crosseal) and are collectively known as fibrin glue. They contain two separate components, freeze-dried clotting proteins (especially fibrinogen) and freeze-dried thrombin, which combine to form a clot. There are numerous studies of fibrin glues with primarily positive results in nonrandomized trials but with indirect endpoints that do not address blood transfusion reduction. A single randomized controlled trial in pediatric patients with coagulopathy demonstrated a marked reduction in blood product use and time in the operating room when fibrin glue was used for local hemostasis [367]. Of interest, Tisseel and Beriplast contain bovine aprotinin, whereas Crosseal contains tranexamic acid. These antifibrinolytic agents slow the breakdown of the artificial clot by limiting generation of plasmin. Aprotinin is a bovine protein that can cause anaphylactic reactions in rare instances. Although aprotinin is not available for intravenous use in the United States, its use in these topical products is unaffected.

Synthetic polymers are used as topical sealants. One compound known as Omnex is a polymer synthesized by combining two monomers of cyanoacrylate. This forms a film over the bleeding site that is independent of the patient's clotting processes. It is fully biodegradable. A randomized controlled study that measured hemostasis at vascular anastomoses in arteriovenous grafts and femoral bypass grafts in 151 patients demonstrated less bleeding with this compound compared with oxidized cellulose [368].

Synthetic polymers of polyethylene glycol (CoSeal and DuraSeal) that cross link with local proteins to form a cohesive matrix sealant that adheres to vascular anastomoses and seals potential bleeding sites. Randomized trials with these commercially available synthetic polymers demonstrated significantly greater immediate sealing in vascular grafts compared with thrombin/gelfoam preparations [369]. These products have limited efficacy against actively bleeding surfaces and use is limited to vascular grafts after anastomotic creation but before the resumption of blood flow.

A sealant composed of bovine albumin and glutaraldehyde is also commercially available. This compound known as BioGlue is dispensed from a double syringe system that dispenses the two compounds with mixing within the applicator tip. The mixture is placed on the repair site creating a seal independent of the body's clotting mechanism. This type of sealant adheres to synthetic grafts by forming a covalent bond to the interstices of the graft matrix. A randomized controlled trial comparing BioGlue with standard pressure control of anastomotic bleeding showed superior hemostasis in the BioGlue group but without evidence of decreased blood transfusion or diminished chest tube bleeding [370]. A significant disadvantage to the use of this compound is the toxicity of glutaraldehyde, with reports of nerve injury, vascular growth injury, and embolization of polymers through graft materials, with subsequent downstream organ damage [371–373]. BioGlue is specifically contraindicated in growing tissue, limiting its use in pediatric procedures. There are anecdotal reports of tissue damage discovered many years after its use [374, 375].

Two new topical sealants (Arista, HemoStase) were recently approved for human use by the FDA without

much direct proof of efficacy in cardiac procedures. Nevertheless, these compounds are approved for most types of surgery including cardiac surgery. These are plant-based compounds with a very large surface area. They are delivered as a powder and are designed to rapidly dehydrate blood by concentrating serum proteins, platelets, and other blood elements on the surface of contact. These compounds are applied to a bleeding surface and are fully absorbed from the wound site within 24 to 48 hours.

Chitin is a naturally occurring polysaccharide polymer used by many living organisms to form a hard crystalline exoskeleton around their soft bodies. Chitin preparations (Celox, HemCon, Chitoseal) form clots in defibrinated or heparinized blood by a direct reaction between Chitin and the cell membranes of erythrocytes. Additionally, Chitin causes the release of local growth factors that promote healing [376]. This topical agent is used as hemostatic dressings for traumatic wounds [377]. A single human case report found that Celox is effective as a topical hemostatic agent in a cardiac procedure [378].

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. There is a distinct need for randomized control trials of the newer agents, especially microporous polysaccharide hemospheres and Chitin-based compounds.

TOPICAL ANTIFIBRINOLYTIC SOLUTIONS

Class IIa.

1. Antifibrinolytic agents poured into the surgical wound after CPB are reasonable interventions to limit chest tube drainage and transfusion requirements after cardiac operations using CPB. (Level of evidence B)

During cardiac procedures using CPB thrombin is generated in the surgical wound mainly by activation of tissue factor [379, 380]. Cell-bound TF is elaborated by cells within the surgical wound and combines with factor VII to form a complex that activates other clotting factors (eg, factors IX and X) to ultimately generate thrombin despite massive doses of heparin and despite multiple attempts to "passivate" the artificial surfaces of the extracorporeal circuit [10, 381, 382]. Thrombin cleaves fibrinogen into fibrin. This process is normally limited by the presence of antithrombin but is rapidly overwhelmed by ongoing wound trauma and the insult of CPB. In the wound, thrombin generation stimulates small vessel endothelial cells at sites of injury to produce tissue-type plasminogen activator, which binds fibrin with high affinity and the zymogen, plasminogen with high specificity [383, 384]. Ongoing thrombin production and fibrinolysis during CPB causes varying levels of consumptive coagulopathy. The wound is also the site of extensive fibrinolysis [385]. High concentrations of fibrin and fibrinogen degradation products are present in shed mediastinal blood [386]. All of these mechanisms highlight the importance of the surgical wound in contributing to perioperative coagulopathy, and suggest that limitation of bleeding should start within the surgical wound during and shortly after CPB.

Two randomized trials and one meta-analysis investigated the efficacy of topical antifibrinolytic agents instilled into the wound after CPB in low-risk cardiac operations [387–389]. In 1993, Tatar and coworkers [387] studied topical aprotinin in 50 elective patients undergoing CABG surgery using CPB. They randomly assigned patients to receive saline or 1 million KIU aprotinin in 100 mL saline poured into the surgical wound immediately before closure. They clamped chest drains during wound closure in the experimental group. Chest drainage within the first 24-hour period was 650 ± 225 mL in the control group and 420 ± 150 mL in the aprotinin group ($p < 0.05$). De Bonis and coauthors [388] found similar benefit of 1 g tranexamic acid poured into the wound at closure in patients having primary coronary arterial bypass. Interestingly, no tranexamic acid could be detected in the circulation 2 hours after CPB ended. Abrishami and coauthors [389] performed a meta-analysis on the topical application of antifibrinolytic drugs used in cardiac procedures using CPB. The meta-analysis of seven trials included 525 first-time cardiac operations, and it was concluded that topical tranexamic acid or aprotinin significantly reduced 24-hour chest drainage [389]. The preponderance of evidence favors topical antifibrinolytic agents, independent of intravenous antifibrinolytics, to limit bleeding related to generation of tissue factor and thrombin in the surgical wound after cardiac procedures using CPB.

h) Management of Blood Resources

SURGICAL TEAMS

Class IIa.

1. Creation of multidisciplinary blood management teams (including surgeons, perfusionists, nurses, anesthesiologists, ICU care providers, housestaff, blood bankers, cardiologists, and so forth) is a reasonable means of limiting blood transfusion and decreasing perioperative bleeding while still maintaining safe outcomes. (Level of evidence B)

There is significant practice variation associated with blood transfusion and management of bleeding in patients having operative procedures [83, 390–392]. This variation persists despite available transfusion and blood management guidelines. For example, many surgeons transfuse blood products based on hemoglobin levels rather than based on patients' clinical status, despite evidence to suggest that clinical bleeding should guide transfusion decisions [393]. There are several reasons why guidelines are not accepted by surgeons [394, 395]. One important component of failure of guideline acceptance is failure to recognize the role of teams in care delivery. In modern medicine, the doctor-patient relationship viewed as a one-on-one interaction is more apparent than real. Teams, not individuals, care for patients in the ICU, in the operating room, and on the

ward. Practice guidelines dealing with blood management during cardiac procedures focus on cardiac surgeons' actions without much consideration for the potential contributions of all members of the health care team. Sharing of responsibilities for blood management among all providers leads to a division of labor that brings other providers into the mix [396]. This is important as key patient events and interventions are often supervised by nonsurgeons (eg, perfusionists, nurses, anesthesiologists, ICU care providers, housestaff, and so forth). Accumulating evidence suggests that nonsurgeon-driven guidelines and protocols are usually more successful than those that rely on surgeons [394, 397]. Multidisciplinary teams make better decisions about postoperative bleeding and blood transfusion, resulting in low transfusion rates and safe outcomes [398–404]. Team building for management of blood resources including transfusion and perioperative bleeding is a reasonable intervention that is likely to provide patient benefit.

7) Summary of Recommendations

A starting point for blood management in patients having cardiac operations is risk assessment. An exhaustive review of the literature suggests three important preoperative risk factors are linked to bleeding and blood transfusion: (1) advanced age (age ≥70 years); (2) low RBC volume either from preoperative anemia or from small body size of from both; and (3) urgent or complex operations usually associated with prolonged CPB time and non-CABG procedures.

Unfortunately, the literature does not provide a good method of assigning relative value to these three risk factors. Nonetheless, these three risks provide a simple qualitative means of stratifying patients according to preoperative risk of bleeding and blood transfusion. Not all patients undergoing cardiac procedures have equal risk of bleeding or blood transfusion. An important part of blood resource management is recognition of patients' risk of bleeding and subsequent blood transfusion. Although there is almost no evidence in the literature to stratify blood conservation interventions by patient risk category, logic suggests that patients at highest risk for bleeding are most likely to benefit from the most aggressive blood management practices. It is necessary to point out that the interventions listed in Table 1 only have evidence to support their use, not necessarily to support their use in each risk category. Blood conservation recommendations among the various risk categories are based on expert consensus of the authors, whereas each of the recommendations in Table 1 has literature support but not necessarily support for each of the risk categories. Table 1 provides a qualitative summary of new or revised recommendations developed in the current document, while Table 2 contains previously published guideline recommendations supported by current evidence in the literature [9]. High-risk patients will likely benefit from interventions in Tables 1 and 2 by conserving valuable blood resources and limiting transfusion.

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Appendix 1

Results of Voting and Dissension Concerns by Members of the Writing Group for Blood Conservation Recommendation

Blood Conservation Intervention	Class of Recommendation (Level of Evidence)	Number in Writing Group Who Agree (Total 17 Voting Members)	Concerns About Recommendation Expressed by Individual Members of Writing Group
Preoperative interventions			
Discontinuation of ADP receptor platelet inhibitors several days before operation depending on drug pharmacodynamics.	I (B)	17	
Use of point-of-care test to assess preoperative platelet ADP receptor inhibition.	IIb (C)	17	
Routine addition of P2Y12 platelet inhibitors to aspirin after CABG.	III (B)	16	• Should be IIb. Not enough evidence demonstrating harm is present. N/A designation due to inadequate data would be more appropriate especially for using nonloading doses in off-pump cases that may have higher risk of postoperative hypercoagulability.
Short-course erythropoietin plus iron a few days before operation (3 to 7 days).	IIa (B)	14	• Should be IIb because of lack of adequate safety data.
Erythropoietin plus iron used with autologous predonation.	IIb (A)	16	• Should be III because of safety concerns.
Drugs used for intraoperative blood management			
Routine use of lysine analogues during cardiac operations using CPB.	I (A)	15	• Should be IIa because of lack of safety data. • Do not believe results of meta-analysis.
Prophylactic high or low dose aprotinin for routine use.	III (A)	16	• Should be IIb as some high-risk patients may benefit from this drug.
Blood derivative used in blood management			
Plasma transfusion for serious bleeding with multiple or single coagulation factor deficiencies when safer products (recombinant/fractions) are not available.	IIa (B)	16	• Should be Class I.
Plasma transfusion for urgent warfarin reversal in a bleeding patient (prothrombin complex concentrate containing adequate factor VII is preferable, if available).	IIa (B)	15	• Should be Class I based on consensus not necessarily published evidence. • Not enough safety data on cardiac surgical patients. Should be IIb.
Plasma transfusion for urgent warfarin reversal in a nonbleeding patient.	III (A)	16	• Should be IIb, not convinced of harm.
Plasma transfusion as part of massive transfusion protocol.	IIb (B)	17	
Prophylactic plasma transfusion.	III (A)	16	• Should be IIb (uncertain harm).
Factor XIII for clot stabilization in a bleeding patient after CPB.	IIb (C)	15	• MS—not enough information (no recommendation). CDM—not enough evidence yet for cardiac patients.
Transfusion with leukoreduced PRBC when blood replacement is required.	IIa (B)	15	• Data support IIb not IIa. • Should be Class I because of safety concerns with nonleukoreduced PRBC.
Use of intraoperative platelet plasmapheresis.	IIa (A)	16	• Risk of technical error significant. Should be III.
Use of recombinant activated factor VII for recalcitrant bleeding.	IIb (B)	16	• Change to Class III based on the safety signal from the RCT (Gill et al).
AT III for heparin resistance immediately before CPB when antithrombin mediated heparin resistance is suspected usually because of preoperative heparin exposure.	I (A)	17	

Continued

Appendix 1. Continued

AT III for patients suspected of having antithrombin depletion when antithrombin mediated heparin resistance is likely usually from preoperative heparin exposure.	IIb (C)	13	• Not enough evidence. • Difficult to operationalize.
Factor IX or products that contain high proportions of factor IX (FEIBA, prothrombin complex concentrate) for recalcitrant perioperative bleeding.	IIb (C)	16	• Should be Class III b/o thrombotic risk and other options available.
Blood salvage interventions			
Expanded use of blood salvage using centrifugation to include patients with known malignancy who require cardiac procedures	IIb (B)	15	• Should be either I or IIa because of efficacy in noncardiac operations.
Pump salvage of residual blood in CPB circuit	IIa (C)	16	• Should be Class I based on consensus.
Centrifugation of pump-salvaged blood, instead of direct infusion, is reasonable for minimizing post CPB allogeneic RBC transfusion	IIb (B)	13	• Should be Class IIa based on evidence.
Minimally invasive procedures			
Use of TEVAR to manage thoracic aorta disease.	I (B)	16	• Should be IIa since no RCTs.
OPCABG to reduce blood transfusion during coronary revascularization.	IIa (A)	17	
Perfusion interventions			
Microplegia to minimize volume of crystalloid cardioplegia and reduce hemodilution.	IIb (B)	16	• Microplegia has minimal effect on blood usage.
Alternate nonheparin anticoagulation in ECMO patients with HIT to reduce platelet consumption.	I (C)	15	• Should expand to include all groups not just ECMO. • Not sure that this should be level I (no reason given).
Minicircuits (reduced priming volume and circuit volume) to reduce hemodilution.	I (A)	16	• Interpretation of data suggests Class IIb not I.
Augmented venous drainage.	IIb (C)	16	• Evidence too sparse and a recommendation should not be made.
Biocompatible CPB circuits to limit hemostatic activation and limit inflammatory response.	IIb (A)	16	• This recommendation seems based on the opinion of Ranucci and colleagues. I suggest recommendation be "Without other measures of blood conservation, biocompatible surface coatings have little clinical benefit." Class IIa Level A
Modified ultrafiltration at the end of CPB.	I (A)	16	• Evidence only supports Class IIa.
Conventional or zero-balance ultrafiltration during CPB.	IIb (A)	16	• Should be Class III—no evidence of benefit.
Leukocyte filters used in the CPB circuit.	III (B)	13	• Recommendation based on limited evidence.
Topical hemostatic agents			
Topical agents that provide anastomotic sealing or compression.	IIb (C)	17	
Topical antifibrinolytic solutions for wound irrigation after CPB.	IIa (B)	17	
Management of blood resources			
Creation of multidisciplinary surgical teams for blood management.	IIa (B)	17	

ADP = adenosine diphosphate; AT = antithrombin; CABG = coronary artery bypass graft surgery; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; OPCABG = off-pump coronary artery bypass graft surgery; PRBC = packed red blood cells; TEVAR = thoracic aortic endovascular repair.

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Appendix 2

Author Disclosures of Industry Relationships

Author	Disclosure	Lecture Fees, Consultant, Paid Work From Industry Within 12 Months	Research Grant Support From Industry Within 12 Months
V. A. Ferraris	No	None	None
S. P. Saha	Yes		Baxter
J. Waters	Yes	Biotronics	Sorin Group
A. Shander	Yes	Bayer, Luitpold, Masimo, Novartis, NovoNordisk, OrthoBiotech, Zymogenetics	Bayer, Novartis, NovoNordisk, Ortho Biotech, Pfizer, ZymoGenetics
L. T. Goodnough	Yes	Eli Lilly, CSL Behring, Luitpold, Amgen	
L. J. Shore-Lesserson	Yes	CSL Behring, Novonordisk	
K. G. Shann	No		
G. J. Despotis	Yes	Genzyme, CSL Behring, Zymogenetics, Bayer, Cubist, SCS Healthcare, Telacris, Eli Lilly, Medtronic, ROTEM, NovoNordisk, Biotrack, HemoTech, Genzyme/GTC	
J. R. Brown	Yes	None	AHRQ K01HS018443 Acute Kidney Injury
J. W. Hammon	Yes	Medtronic, St. Jude Medical	
C. D. Mazer	Yes	NovoNordisk, Oxygen Biotherapeutics, Cubist	NovoNordisk, Cubist
R. A. Baker	Yes		Terumo Cardiovascular; Lunar Innovations; Cellplex Pty Ltd, Somanetics
D. S. Likosky	Yes		AHRQ, Maquet Cardiovascular, Somanetics Corporation; Sorin Biomediça; Terumo Cardiovascular Systems, Medtronic
T. A. Dickinson	Yes	SpecialtyCare, Inc	
D. J. FitzGerald	No		
H. K. Song	Yes		Novo Nordisk A/S
T. B. Reece	No		
M. Stafford-Smith	Yes	PolyMedix, Inc	
E. R. Clough	No		