Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline*

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Background. A minority of patients having cardiac procedures (15% to 20%) consume more than 80% of the blood products transfused at operation. Blood must be viewed as a scarce resource that carries risks and benefits. A careful review of available evidence can provide guidelines to allocate this valuable resource and improve patient outcomes.

Methods. We reviewed all available published evidence related to blood conservation during cardiac operations, including randomized controlled trials, published observational information, and case reports. Conventional methods identified the level of evidence available for each of the blood conservation interventions. After considering the level of evidence, recommendations were made regarding each intervention using the American Heart Association/American College of Cardiology classification scheme.

Results. Review of published reports identified a high-risk profile associated with increased postoperative blood transfusion. Six variables stand out as important indicators of risk: (1) advanced age, (2) low preoperative red blood cell volume (preoperative anemia or small body size), (3) preoperative antiplatelet or antithrombotic drugs, (4) reoperative or complex procedures, (5) emergency operations, and (6) noncardiac patient comorbidities. Careful review revealed preoperative and perioperative interventions that are likely to reduce bleeding and postoperative blood transfusion. Preoperative interventions that are likely to reduce blood transfusion include identification of high-risk patients who should receive all available preoperative and perioperative blood conservation interventions and limitation of antithrombotic drugs. Perioperative blood conservation interventions include use of antifibrinolytic drugs, selective use of off-pump coronary artery bypass graft

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> See Appendix 1 for authors' financial relationships with industry.

surgery, routine use of a cell-saving device, and implementation of appropriate transfusion indications. An important intervention is application of a multimodality blood conservation program that is institution based, accepted by all health care providers, and that involves well thought out transfusion algorithms to guide transfusion decisions.

Conclusions. Based on available evidence, institution-specific protocols should screen for high-risk patients, as blood conservation interventions are likely to be most productive for this high-risk subset. Available evidence-based blood conservation techniques include (1) drugs that increase preoperative blood volume (eg, erythropoi-

etin) or decrease postoperative bleeding (eg, antifibrinolytics), (2) devices that conserve blood (eg, intraoperative blood salvage and blood sparing interventions), (3) interventions that protect the patient's own blood from the stress of operation (eg, autologous predonation and normovolemic hemodilution), (4) consensus, institution-specific blood transfusion algorithms supplemented with point-of-care testing, and most importantly, (5) a multimodality approach to blood conservation combining all of the above.

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1) Methods Used in Developing Guidelines

Table 1 describes the methods used to quantify the types of evidence available to answer relevant questions and the classification system used to summarize recommendations about clinically important questions. This classification system is the same as that used by the Joint Task Force for Guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA [available at: http://circ.ahajournals.org/manual/manual_IIstep6.shtml]).

It is apparent that any medical or surgical intervention has both systematic and random effects, some of which are beneficial and some of which are not. The practice of medicine often necessitates a probabilistic balancing of these conflicting effects, recognizing that there will always be a residual level of uncertainty. Jenicek [1] sum-

marizes this probabilistic approach as follows: ". . . the science of medicine becomes a structured and organized way of using probability, uncertainty, and facts in preventive medicine and clinical care to best benefit the patient and the community."

Evidence-based guidelines are an attempt to reconcile often conflicting lines of evidence, giving greater weight to evidence derived from more methodologically rigorous studies and those for which the overall weight of evidence is most convincing. They must be viewed as guidelines and recommendations, not absolutes. With this in mind, the authors searched numerous sources for available evidence about specific questions relating to the use of blood transfusions and blood conservation before, during, and after cardiac operations.

The committees from The Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA) participated in guideline development. The committee members' financial relationships with industry are listed in Appendix 1. Appendix 2 outlines the steps employed in development of the final guideline document. Within these guidelines, cost analysis was not a primary consideration in formulating the recommendations. Costs change constantly depending upon markets and other forces. The science was the focus, and the risks and benefits from bleeding and blood transfusion should not vary with societal economic forces.

Abbreviations and Acronyms	
ACC	= American College of Cardiology
ACT	= activated clotting time
ADP	= adenosine diphosphate
AHA	= American Heart Association
ANH	= acute normovolemic hemodilution
ASA	= American Society of Anesthesiologists
CABG	= coronary artery bypass graft surgery
CPB	= cardiopulmonary bypass
CUF	= conventional ultrafiltration
DDAVP	= desmopressin acetate
EACA	= epsilon-aminocaproic acid
EPO	= erythropoietin
GPI	= glycoprotein inhibitor
HIV	= human immunodeficiency virus
ICU	= intensive care unit
LMWH	= low-molecular-weight heparin
MUF	= modified ultrafiltration
NIH	= National Institutes of Health
OPCAB	= off-pump coronary artery bypass
PEEP	= positive end-expiratory pressure
RCT	= randomized controlled trial
SCA	= Society of Cardiovascular Anesthesiologists
STS	= The Society of Thoracic Surgeons
TQM	= total quality management
TXA	= tranexamic acid

2) Risks and Benefits of Blood Transfusion—the Dilemma

Class IIa

1. **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)**

Arguably, the practice of modern transfusion medicine began with the discovery of blood groups by Landsteiner. Even though his work won the Nobel Prize in 1930, the full impact of his discovery lagged; and other developments such as arterial anastomosis (Carrel), blood component therapy, refrigeration of blood components, or-

Table 1. Classification Scheme Used to Summarize Clinical Recommendations[a]

	Class I	Class IIa	Class IIb	Class III
Estimate of certainty (precision) of treatment effect	Benefit >>> Risk Procedure/treatment SHOULD be performed/administered.	Benefit >> Risk: additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/ administer treatment.	Benefit ≥ Risk: additional studies with broad objectives needed; additional registry data would be helpful. IT IS NOT UNREASONABLE to perform procedure/administer treatment.	Risk ≥ Benefit: no additional studies needed. Procedure/treatment should NOT be performed/ administered AS IT IS NOT HELPFUL AND MAY BE HARMFUL.

Level A
  Multiple (3–5) population risk strata evaluated
  General consistency of direction and magnitude of effect
	Recommendation that procedure or treatment is useful/effective
	Sufficient evidence from multiple randomized trials or meta-analyses
		Recommendation in favor of treatment or procedure being useful/effective
		Some conflicting evidence from multiple randomized trials or meta-analyses
			Recommendation's usefulness/efficacy less well established
			Greater conflicting evidence from multiple randomized trials or meta-analyses
				Recommendation that procedure or treatment not useful/effective and may be harmful
				Sufficient evidence from multiple randomized trials or meta-analyses

Level B Limited (2–3) population risk strata evaluated	Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or nonrandomized studies	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies	Recommendation that procedure or treatment not useful/effective and may be harmful Limited evidence from single randomized trial or nonrandomized studies
Level C Very limited (1–2) population risk strata evaluated	Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard-of-care	Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care	Recommendation's usefulness/efficacy less well established Only expert opinion, case studies, or standard-of-care	Recommendation that procedure or treatment not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care

[a] Taken from the the AHA/ACC Manual for Guideline Writing Committees at http://circ.ahajournals.org/manual/manual_llstep6.shtml.

Table 2. Risks of Blood Transfusion

Type	Occurrence in Red Blood Cell Units Transfused
Infectious	
Human immunodeficiency virus [669, 670]	1 in 1.4–2.4 × 10^6
Hepatitis B [669]	1 in 58,000–149,000
Hepatitis C [670]	1 in 872,000–1.7 × 10^6
Bacterial infection [671]	1 in 2,000
Immunologic reactions	
Febrile nonhemolytic transfusion reactions [672–675]	1 in 100
Anaphylactic transfusion reactions [676]	1 in 20,000–50,000
ABO mismatch [677]	
Hemolysis	1 in 60,000
Death	1 in 600,000
Leukocyte-related target organ injury [3–5, 678]	1 in 20 to 1 in 50
Transfusion-related acute lung injury [679]	1 in 2000
Post-transfusion purpura [680]	Rare
Transfusion services error	
Donor screening error [669] (malaria, *T cruzi*, babesioses, Creutzfeld-Jakob disease)	1 in 4 × 10^6
Transfusion services error [681]	1 in 14,000

ganization of blood banks, use of anticoagulation, and the urgency of treating war-injured patients were necessary to bring transfusion into the modern era.

As early as 1943, it was recognized that blood transfusion could spread diseases, especially hepatitis [2]. Since that time, other problems such as risks associated with paid donors and concerns about disease transmission, including the current epidemic of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and transmission of hepatitis C, raised awareness of the problems associated with blood transfusion (Table 2), almost to the point that the benefits of blood transfusion are overlooked. It is important to realize that the viral and parasitic infectious risks of blood transfusion are dramatically increased in third-world countries or in areas where modern blood banking practices are not available (http://www.cochrane.org/reviews/en/ab002042.html).

Transfusion of red cells causes immunomodulation, although the extent and type of immune deficit is controversial. In some blood banks, leukocyte reduction of red cells is used routinely. With non–leukocyte reduced transfusions in randomized trials, multiorgan failure and death occur in as many as 10% of transfused intensive care unit (ICU) patients, versus 5% in recipients of leukocyte reduced transfusions [3–5]. Transfusion-related acute lung injury may be the most common complication of transfusion, although this remains controversial. As many as 1 in 20 patients experienced a transfusion-related death in some studies [3–5]. Blum-

berg and coworkers [3] suggest that as many as 1 in 40 or 50 patients receiving non–leukocyte reduced transfusions died in excess of that seen in recipients of leukocyte reduced transfusions. The added cost of leukocyte reduction may limit universal acceptance of this technique, but there is some evidence that red cell transfusion-related immunomodulation is a cause of significant morbidity, and this morbidity may be reduced by leukocyte reduction of red cells.

It is difficult to define the benefits of blood transfusion, as randomized trials to support the use of blood products to treat disease do not exist. Blood transfusion was accepted long before the complications associated with transfusion could be documented. Many traumatic injuries (especially war-related injuries) were almost universally fatal before the advent of blood transfusion. The practice of blood transfusion saved countless lives long before the complications of this therapy were recognized [6].

Enhanced oxygen-carrying capacity [7], improved hemostasis associated with blood component therapy [8, 9], and volume support of cardiac output are three accepted benefits of blood transfusion. Adams and associates, in 1942 (through the pioneering blood banking work of John Lundy) [10, 11], on the basis of clinical observations [10] and animal studies [11], introduced the "10/30" rule of blood transfusion. These authors suggested that the minimal ideal level of oxygen-carrying capacity is maintained by a hematocrit of around 30% and hemoglobin of 10 g/dL. Because of the risks of transfusion with associated costs, and lack of clear evidence regarding the benefit of blood transfusion, the 10/30 arbitrary rule has fallen into disfavor.

There is lack of clear evidence regarding the benefit of blood transfusion. However, clinical reports [12–14] of survival benefit support transfusion in certain clinical situations. A task force of the American Society of Anesthesiologists (ASA) developed a consensus statement based mostly on level B and C evidence that concluded that "red blood cell transfusions should not be dictated by a single hemoglobin 'transfusion trigger' but instead should be based on the patient's risk of developing complications of inadequate oxygenation" [15]. They developed guidelines for transfusion of packed red cells in adults that were accepted by others without much argument and with little high-level evidence to support them. Their guidelines are listed in Table 3. The ASA guidelines do not specifically address the uniqueness of the cardiac surgery patient. Revised ASA guidelines are available on line at: http://www.asahq.org/publicationsAndServices/BCTGuidesFinal.pdf. Because of the lack of randomized trials to define the role of blood transfusion in cardiac surgery and because of concerns about complications of blood transfusion, it is reasonable to review the available evidence supporting transfusion decisions for cardiac operations. The aim of this review is to provide clinically useful guidelines, based on available evidence, to aid cardiothoracic surgeons and an-

Table 3. American Society of Anesthesiology Guidelines for Transfusion of Packed Red Cells in Adults [682]

- Transfusion for patients on cardiopulmonary bypass with hemoglobin level ≤ 6.0 g/dL is indicated [173, 174, 683, 684].
- Hemoglobin level ≤ 7.0 g/dL in patients older than 65 years and patients with chronic cardiovascular or respiratory diseases justifies transfusion [177, 685].
- For stable patients with hemoglobin level between 7 and 10 g/dL, the benefit of transfusion is unclear [7, 174, 175].
- Transfusion is recommended for patients with acute blood loss more than 1,500 mL or > 30% of blood volume.
- Evidence of rapid blood loss without immediate control warrants blood transfusion.

esthesiologists in their decisions about blood conservation and transfusion.

3) Causes of Blood Transfusion After Cardiac Operations

a) The "High-Risk" Patient

In formulating evidence-based guidelines, it is reasonable to identify high-risk subsets of patients who consume most of the blood products during and after operation and who are the most likely to benefit from blood conservation interventions. A typical profile of transfusion for a cardiac practice is shown in Figure 1 [16]. There are at least three remarkable features of Figure 1. First, more than 50% of patients undergoing cardiac procedures receive no allogeneic blood transfusion. Second, patients who receive more than 10 donor units of blood products are in the 90th percentile of the patient transfusion profile. Third, 10% to 20% of patients consume about 80% of the total blood product transfusions in this population. Consistently, there is a high-risk subset of patients who require large amounts of blood products during their cardiac procedures. By identifying high-risk patients and altering transfusion practices in this group,

the variability in transfusion practices is expected to trend toward standard levels and ultimately conserve valuable resources.

b) Multivariate Predictors and Observational Variables Associated With Blood Transfusion

Class I

1. **Preoperative identification of high-risk patients (advanced age, preoperative anemia, small body size, non–coronary artery bypass graft surgery [CABG] 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)**

Numerous reports identify multivariate predictors of postoperative bleeding and blood transfusion after cardiac operations. Additionally, multiple publications document anecdotal or observational reports of acquired, congenital, or process variables associated with increased bleeding. Table 4 is a summary of these publications with the variables separated by patient-related, procedure-related, and process-related factors. Very few studies listed in Table 4 differentiate between red blood cell transfusion and non–red cell hemostatic factor transfusion. Wherever this distinction was made, it was taken into account in the table. A minority of the studies listed in the table provide odds ratios or *p* values to support the strength of a particular risk factor as a predictor of blood transfusion. As a consequence, the factors are simply listed without an attempt to add a quantitative measure to each risk factor. Many of the risk factors in Table 4 are listed as a single factor, although it is realized that the risk may be a spectrum spanning low to high intensity. For example, the risk associated with age greater than 75 years is significantly greater than risk for a patient aged
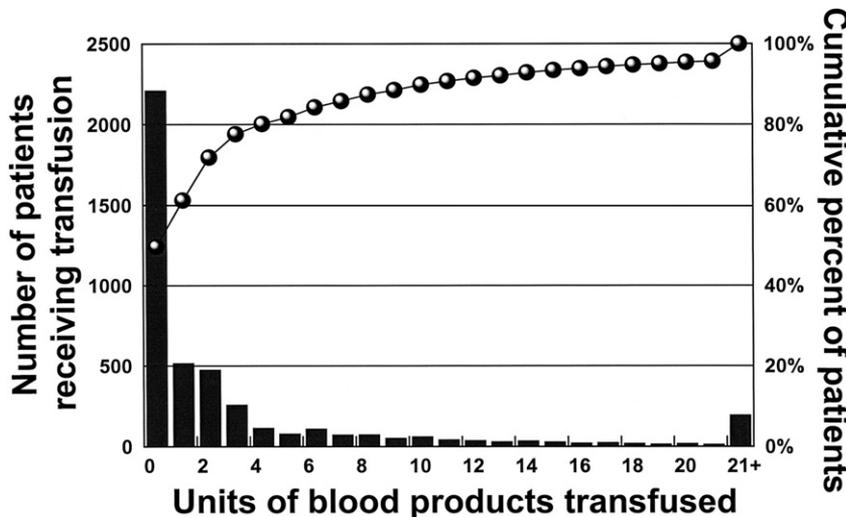

Fig 1. Pareto diagram of the distribution of nonautologous blood units transfused in 4,445 cardiac surgical patients during a 4-year period. Eighty-six percent of the units transfused are consumed by 20% of the patients who receive more than 10 donor units per operation. (Bars = frequency; balls = cumulative percent.)

Table 4. Multivariate and Observational Risk Factors Associated With Increased Bleeding or Blood Transfusion During or After Cardiac Operations

Risk Factor	References Suggesting Risk Factor Is Related to Transfusion of Red Blood Cells	References Suggesting Risk Factor Is Associated With Transfusion of Non–Red Blood Cell Hemostatic Components
Patient-related variables		
Advanced age or age more than 70 years	20, 26, 28, 143, 467, 686–692	377, 687, 693
Preoperative anemia	7, 20, 26, 28, 49, 143, 526, 686, 688, 689, 691, 694, 695	7, 693, 695
Female gender	26, 28, 86, 143, 467, 686, 688, 693, 696	76, 86, 377, 686, 688, 693, 697
Body size or body surface area	20, 26, 28, 49, 86, 143, 166, 467, 686, 688, 691, 692	166, 691
Preoperative antithrombotic therapy		
High intensity (abciximab, clopidogrel, direct thrombin inhibitors, low-molecular-weight heparin, long-acting direct thrombin inhibitors, thrombolytic therapy)	54, 81, 103–107, 124, 125, 698–712	54, 81, 104–107, 467, 698–701, 703–705, 707–709, 712–715
Low intensity (aspirin, dipyridamole, eptifibatide, tirofiban)	17, 18, 87, 90, 467, 702, 716–722	17, 18, 87, 89, 90, 377, 717, 719, 720, 722
Preoperative coagulopathy		
Hereditary coagulopathy or platelet defect (von Willebrand's disease, Hermansky-Pudlak, Bernard-Soulier, Scott, Werlhof, Glanzmann's, hemophilia A or B, clotting factor deficiencies, etc)	22, 723–735	22, 723–735
Acquired coagulopathy or platelet abnormality (nonspecific platelet defect measured by template bleeding time or PFA-100, chronic lymphocytic leukemia, cirrhosis, lupus anticoagulant, drug-related polycythmia vera, myelodysplastic syndrome, ITP, beta thalassemia, etc).	20, 21, 23, 25, 49, 736–741	21, 23, 25, 736–741
Cardiogenic shock, congestive heart failure, or poor left ventricular function	28, 143, 689, 691, 695	691
Renal insufficiency	28, 49, 691	691
Insulin-dependent adult-onset diabetes mellitus	28, 742	28, 49, 76, 143, 697, 743
Peripheral vascular disease	28	
Preoperative sepsis	744, 745	744, 745
Liver failure or hypoalbuminemia	28, 746	746
Procedure-related variables		
Prolonged CPB time	45, 49, 377, 526, 686, 691–693, 695, 747	377, 691, 693
Reoperation	28, 143, 377, 467, 689	377, 691
Type of operation (other [aortic, complex, etc] > valve/CABG > valve > CABG)	377, 467, 695, 747	377
Increased protamine dose after CPB	377	377
Increased cell-saving volume	377	377
Intraoperative autologous donation	526, 693	693
Need for transfusion while on CPB	377, 686, 687, 695	377, 686, 687, 695
Use of polymerized starch for volume expansion	686, 748	686, 748
Process-related variables		
Lack of transfusion algorithm with point-of-care testing	45, 276, 654–659, 749–752	276, 654–659, 751, 752
Use of internal mammary artery (either one or two)	747	
Reduced heparin dose	753	753
Low body temperature in intensive care unit	377	377

CABG = coronary artery bypass graft surgery;   CPB = cardiopulmonary bypass;   ITP = idiopathic thrombocytopenic purpura.

55 years or younger, and it is quite likely that the risk of transfusion associated with age is not a continuous function. Likewise, the risk associated with some antithrombotic drugs (eg, aspirin) is low on the risk spectrum while that of others (eg, clopidogrel) is much higher. No attempt was made to measure the risk spectrum of variables listed in Table 4 as the evidence base for these variables as risk factors is limited and few quantitative descriptors of risk are available.

The studies listed in Table 4 are far too heterogeneous to lend themselves to meta-analyses. The level of evidence in most cases is low, but consensus was used to assign importance to each of these predictor variables. Within each of the three major categories (patient-related, procedure-related, or process-related), the variables are arranged in descending order of importance. Certain of the variables stand out as high-risk predictors including advanced age, preoperative anemia or small body size (ie, low red blood cell volume), the duration or urgency of operative intervention, the presence of antiplatelet or antithrombotic drugs taken shortly before operation, and the presence of multiple noncardiac comorbidities (eg, renal failure, diabetes mellitus, acquired or congenital coagulopathy, and so forth). Any of these common risk factors should alert the clinician to bleeding risk and should trigger blood conservation measures aimed at addressing the specific risks (see below).

Special clinical situations call for special interventions and should be "red flags" for surgeons faced with these problems. Patients with acquired or congenital coagulopathies, patients scheduled for complex procedures (eg, combined valve/coronary revascularization, aortic dissection with deep hypothermic circulatory arrest), repeat cardiac procedures, sepsis with thrombocytopenia, and Jehovah's Witnesses fall into this category.

c) Patient-Related Causes of Bleeding
Class IIa

1. **Patients who have thrombocytopenia (less than 50,000/mm²), 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 group at high risk for bleeding. Maximum blood conservation interventions during cardiac procedures are reasonable in these high-risk patients. (Level of evidence B)**

There is evidence that certain patients have an accentuated response to the usual doses of antiplatelet drugs [17]. Certain "hyperresponders" to average doses of aspirin exhibit very prolonged skin bleeding times [18–20]. This accentuated response to aspirin may result in increased perioperative blood loss worsened by preoperative antiplatelet therapy. The mechanisms of these accentuated effects of aspirin and other antiplatelet drugs are undoubtedly related to individual pharmacogenomic variation and involve the antiplatelet, antiinflammatory, anticoagulant, and endothelial-protecting actions of these agents.

Patients with thrombocytopenia from whatever cause (defined as platelet count below 50,000) are at extremely high risk of excessive bleeding after CABG [21–25]. Additionally, patients with preoperative anemia (eg, renal failure, repeated blood drawing during prolonged ICU stay, multiple recent percutaneous procedures, and so forth) exhibit increased perioperative blood transfusion [20, 26–28]. One of the earliest observations about anemia was that bleeding time was prolonged in anemic patients [29, 30]. Anemia-related bleeding abnormalities are likely to be worsened by antiplatelet drugs [17].

Patients with other congenital or acquired qualitative platelet defects are at increased bleeding risk [26–28, 31–37]. Congenital defects include vonWillebrand's disease, Bernard-Soulier syndrome, Glanzmann's thrombasthenia, storage-pool disease, and others. Acquired qualitative defects are seen in liver disease, renal disease and drug induced qualitative platelet defects.

d) Physician-Related Causes of Bleeding
There is no doubt that physician practices influence bleeding and blood transfusion. Surgical practices differ widely and can dramatically influence perioperative bleeding and transfusion. Regardless of the patient's condition at operation or immediately postoperatively, physicians do not consistently apply the same triggers or indications for ordering blood transfusions. Use of transfusions varies widely among centers [38–41]. Stover [2] showed the institution as well as the individual physician are independent multivariate risk factors for allogeneic transfusion. Practice variability in the transfusion of blood products impacts resource utilization [42]. Johnson and associates [43] describe the comparison of outcomes with two different transfusion strategies (conservative versus liberal), and they concluded that no specific transfusion trigger was justified but that the important indicator for transfusion should be patient symptoms and clinical condition. Variation in cardiopulmonary bypass practices, including time on bypass, influences platelet function and perioperative bleeding [44, 45]. Differences in practice patterns relative to recognition, correction, and exploration for excessive postoperative hemorrhage also contribute to wide variability in transfusion practices [46, 47].

e) Procedure-Related Causes of Bleeding
It is difficult to separate the procedure-related variables from those that are the result of physician practices, but certain procedure-related factors stand out. Repeat procedures have higher transfusion rates [48], and the type and urgency of operation are independent predictors for transfusion [49]. Hypothermia related to cardiopulmonary bypass influences platelet function and coagulation [50–52], and the effect can persist into the ICU [53]. Off-pump cardiac surgery is associated with an overall reduction in transfusion requirements [54–56]. Of the coronary artery bypass surgery patients, those who have bilateral internal mammary artery grafts suffer a greater postoperative blood loss than saphenous vein or single mammary artery graft patients [57]. Replacement of the

aortic valve with a pulmonary autograft (Ross procedure) is a technically challenging operation, with up to 20% incidence of postoperative bleeding necessitating reexploration [58] and above average mortality rate [59]. Hemostatic dysfunction and concomitant coagulation abnormalities are often seen in candidates for and recipients of ventricular assist devices or artificial hearts [60–62]. These procedure-related variables influence perioperative bleeding and should alert the surgeon and anesthesiologist to additional risk.

f) Drug-Related Causes of Bleeding

Class IIa

1. **It is reasonable to discontinue thienopyridines 5 to 7 days before cardiac procedures to limit blood loss and transfusion. Failure to discontinue these drugs before operation risks increased bleeding and possibly worse outcome. Caution must be used with sudden withdrawal of antiplatelet therapy in the presence of drug-eluting stents. That can lead to stent thrombosis, and the surgical team should consider various alternatives to maintain stent patency. That could even include hospitalization to convert thienopyridine therapy to short-acting GP2b/3a inhibitors for a few days before operation. (Level of evidence B)**
2. **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)**

Class IIb

1. **Most high-intensity antithrombotic and antiplatelet drugs (including ADP-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. It is not unreasonable to stop these medications before operation to decrease minor and major bleeding events. The timing of discontinuation depends on the pharmacodynamic half-life for each agent as well as on the potential lack of reversibility. Unfractionated heparin is a notable exception in that it is the only agent that may be discontinued shortly before operation or not at all. (Level of evidence C)**

Class III

1. **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)**

Drug therapy has a growing role and influence in the prevention and treatment of cardiovascular disease. Many of the active cardiac drugs provide benefit by inhibiting platelet function, or by causing clot lysis. Thus,

any surgical procedure required in the face of such drugs poses a greater than normal risk of perioperative hemorrhage and transfusion requirement. A large body of literature defines the risk/benefit relationship of antiplatelet and anticoagulant drugs, and this subject is covered in detail below.

Stent implantation in coronary arteries and in saphenous vein grafts is accompanied by guideline-driven pharmacologic therapy to maintain patency and prevent thrombo-occlusion [63–66], but with a relatively high incidence of bleeding and vascular complications [67, 68]. Hemorrhagic complications occur at reported rates between 1.9% and 9.8% after placement of stents, with worse outcome among patients receiving transfusions during stent implantation [69–73]. Other studies show even higher rates of bleeding complications, at 21.8% to 27.4%, with varying frequency of blood transfusion ranging between 0% and 9.5% [74, 75].

Preoperative antiplatelet and anticoagulant treatment as prophylaxis for coronary occlusive disease is associated with excessive intraoperative and postoperative bleeding as well as resultant transfusion, in most [20, 76–81], but not all situations [82–86]. Therefore, this aspect of patients' preoperative medication regimens must be managed for maximum cardioprotective benefit, while minimizing risk of hemorrhagic complication. Guidelines are available to aid in this decision process [87]. Patients with thrombocytopenia or with qualitative platelet defects (eg, renal failure, vonWillebrand's disease, anemia, and so forth) are particularly sensitive to antiplatelet drugs and represent a high-risk subset that require multiple blood conservation interventions to minimize blood loss and transfusion. Discontinuation of antiplatelet and antithrombotic drugs before CABG in these high-risk patients is prudent.

There is evidence that certain patients have an accentuated response to the usual doses of preoperative aspirin [17]. Certain "hyperresponders" to average doses of aspirin exhibit very prolonged skin bleeding times [18, 19]. This accentuated response to aspirin may result in increased perioperative blood loss [17]. The mechanisms of these effects of aspirin are undoubtedly multifactorial and include the antiplatelet, antiinflammatory, anticoagulant, and endothelial-protecting actions of aspirin. For the vast majority of patients with acute coronary syndromes who require urgent CABG, the best option seems to be to continue aspirin until operation [88]. For the elective patient who requires CABG and does not have an acute coronary syndrome, it may be reasonable to discontinue aspirin for a few days (2 to 3 days) with the expectation that there will be less perioperative bleeding and blood transfusion.

Dipyridamole reduced postoperative blood loss and transfusions in one study, and was thought to preserve platelets during operative intervention [89]. Dipyridamole and aspirin in combination increased bleeding compared to placebo or aspirin alone [90–93], and graft occlusion was reduced, but not eliminated [94]. Breyer and associates [95] demonstrated increased incidence of delayed postoperative cardiac tamponade with rou-

tine perioperative administration of aspirin and dipyridamole. According to the Antithrombotic Trialists' Collaboration, the addition of dipyridamole to aspirin adds no significant benefit over aspirin alone and may increase bleeding risk [96].

Thienopyridines are a class of antiplatelet drugs that reduce adenosine diphosphate (ADP)–mediated platelet activation, with significant improvement of clinical outcomes in many coronary and cardiovascular conditions. Ticlopidine was the first available thienopyridine, but initially, widespread use was limited by frequent side effects, as well as neutropenia and thrombotic thrombocytopenic purpura [97–99]. In contrast, clopidogrel has a much better safety profile, and has become standard therapy after coronary stent implantation [97]. Because clopidogrel is so well tolerated, and pretreatment before stent implantation is advantageous to coronary artery patency, it is a common occurrence that patients undergoing urgent or emergent coronary artery bypass surgery have recent exposure to dual antiplatelet therapy of clopidogrel and aspirin. This dual therapy, although safe and effective during coronary intervention [100–103], results in higher postoperative bleeding, more transfused blood products, and higher rate of reexploration for mediastinal hemorrhage during emergency CABG [104–107]. To address this disturbing finding, Ley [108] described the implementation of a quality improvement initiative around preoperative exposure to clopidogrel. The current ACC/AHA guidelines and the current STS guidelines recommend discontinuing ADP-inhibitors 5 to 7 days before cardiac operations, if possible, recognizing that operations sooner than 5 days in patients on ADP-inhibitors risk increased perioperative bleeding and transfusions and possibly worse long-term outcomes [87, 109]. However, with the new drug-eluting stents sudden withdrawal of platelet inhibition appears to cause thrombotic risk [110, 111]. The drug-eluting stents exhibit delayed endothelialization compared with bare metal stents, and once platelet inhibition is removed, the foreign surface inside the vessel wall creates a nidus for platelet and white cell activation as well as a potential for hypersensitivity reaction [112, 113]. Minimal evidence is available to guide therapy in this situation. Consensus favors some element of platelet inhibition in the patient who requires CABG but has a coated stent in place. Discussion with all members of the cardiovascular team including cardiologists, hematologists, and the operating team is essential. Possible alternatives include shifting to a short half-life glycoprotein IIb/IIIa inhibitor (GPI) or to a direct thrombin inhibitor while waiting for the effects of thienopyridines to disperse, but more evidence is required to determine the best option.

Platelet GPIs, introduced a decade ago, play a profound role in abolition of platelet aggregation and platelet thrombus formation, and reduce the risk of acute ischemic complications after coronary occlusion and coronary angioplasty. Coller and colleagues [114] reported

an approximately twofold increased risk of major bleeding in patients treated with abciximab. Short-acting GPIs, tirofiban and eptifibatide, in combination with aspirin and heparin, are used during coronary intervention without a significant increase in serious catheterization-related bleeding events [115–117]. The longer acting GPI, abciximab, improves the clinical outcome of percutaneous coronary intervention, but causes thrombocytopenia and access site bleeding [118, 119]. Tirofiban and abciximab have comparable efficacy and bleeding complications [120]. Limited evidence is available to guide the use of GPIs in patients with acute myocardial infarction or with unstable coronary syndromes who also need cardiac operations [87, 109]. These patients should be considered at high risk for bleeding and blood transfusion, and clinical judgment regarding timing of intervention and transfusion needs is likely the most important determinant of outcomes. Again, guidelines based on consensus agreement are available to assist in this decision analysis [87].

Heparin is an integral component of therapy for acute coronary events. Systematic review of six randomized controlled trials looking at heparin in patients with acute myocardial infarction treated with thrombolytic therapy showed severe bleeding to be similar between those receiving and not receiving heparin [121]. Low-molecular-weight heparins (LMWH) have an acceptable risk of bleeding in management of unstable angina [122], and short-term unfractionated heparin or LMWH is used in acute coronary syndromes. Low-molecular-weight heparin after coronary artery stenting had a 10.5% incidence of hematomas or false aneurysm, and a 3.25% incidence of blood transfusion or surgical repair [123]. One study showed hemorrhage and reexploration for bleeding after CABG to be significantly higher in patients receiving enoxaparin versus unfractionated heparin—but the timing of preoperative dosing is not described in this report [124]. Patients receiving LMWH within 12 hours of cardiac surgery have significantly greater blood loss and increased blood transfusion compared with patients receiving intravenous heparin or a dose of LMWH more than 12 hours before operation [125]. Medalion and associates [126] showed that enoxaparin administered more than 8 hours before coronary artery bypass surgery is not associated with increased postoperative bleeding or transfusion requirement.

Despite the almost universal use of unfractionated heparin, especially during cardiopulmonary bypass, there remains concerns with this drug including heparin rebound, heparin resistance, protamine reaction, heparin-induced thrombocytopenia, and heparin-induced platelet dysfunction [127, 128]. Investigation of alternatives to unfractionated heparin resulted in the availability of some direct-acting thrombin inhibitors (eg, hirudin, bivalrudin, and argatroban) to limit thromboses in patients with cardiovascular disease. Potential advantages of direct thrombin inhibitors include a more predictable anticoagulant response than heparin. Based on randomized trials direct thrombin

inhibitors are superior to heparin in preventing arterial thromboses. For example, hirudin is superior to heparin in patients with acute myocardial infarction [129], but safety concerns about increased bleeding and inability to monitor anticoagulation limit use of this agent. The shortest acting direct thrombin inhibitor, bivalirudin, has a half-life of 25 minutes, while that of argatroban is 45 minutes, hirudin 60 minutes, and ximelagatran 3 hours. All of the direct thrombin inhibitors are plagued by the lack of reversibility, difficulties in monitoring the level of anticoagulation, and a prolonged half-life compared with heparin. Argatroban is cleared mainly by the liver, and its use is limited in patients with hepatic dysfunction, but may be preferred for treatment of heparin-induced thrombocytopenia in patients with renal dysfunction.

Experience with direct thrombin inhibitors is limited in patients having cardiac procedures after coronary interventions [134]; however, a recent controlled randomized trial using bivalirudin during off-pump coronary artery bypass surgery (OPCAB) suggests that bivalirudin is safe and effective as an anticoagulant during OPCAB [135]. Likewise, argatroban was used as an anticoagulant during OPCAB with satisfactory results [136]. Lack of a ready reversibility for direct thrombin inhibitors is a major limitation, especially with longer acting agents, and can lead to catastrophic bleeding when used in patients requiring CPB [137]. Bivalirudin is at least as effective as heparin in ischemic heart disease, but with significant reduction in major hemorrhage [130–133]. The Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-1 trial compared bivalirudin and heparin in patients undergoing percutaneous coronary interventions, and compiled a large prospective dataset of bivalirudin administered concomitantly with planned GPIs. Occurrence of major bleeding was comparable between bivalrudin and heparin in nonoperated patients, but experience with this agent is limited in patients having cardiac procedures [134]. The Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial reported improved outcome with decreased bleeding for percutaneous coronary intervention patients who received bivalirudin compared with unfractionated heparin. Trials of bivalirudin for off pump and on pump cardiac surgery showed equivalent 30 day success rates compared with unfractionated heparin [138–140]. Bleeding was not dramatically different, although there appeared to be a tendency for early reexploration of the patients with bivalirudin, as this was an unblinded series of studies. One study from New Zealand showed that graft flow in off-pump CABG patients who received bivalirudin was better than in patients receiving unfractionated heparin for on-pump CABG [135]. Bivalirudin may prove most helpful in patients with heparin induced thrombocytopenia who require coronary revascularization or other cardiac procedures [141].

4) Indications for Blood Transfusion—"Transfusion Trigger"

a) General Considerations

The indications for blood product transfusion in cardiac surgery include treatment of coagulopathies and correction of anemias with the ultimate goal of limiting bleeding and improving oxygen-carrying capacity. The indications for transfusions evolved significantly since the early 1940s when subjective indications were developed to address these theoretical considerations. In the modern era, the overall risk and benefit relationships of blood transfusion therapy weigh the possible benefit of improved tissue oxygenation with the risk of transmitting blood-related diseases or inducing adverse reactions. The economic impact and cost of transfusion therapy in an environment in which blood can be a life-saving, yet scarce resource, mandates a careful understanding of the indications for blood transfusion and the development of appropriate decision-making processes in this regard. The ultimate goal of any discussion regarding the indications for blood component therapy is to maximize patient benefit and limit risk when possible. A great deal is known with regard to blood transfusion risks yet little is known of its benefits.

b) Transfusion Triggers
Class IIa

1. **With hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable, as 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)**
2. **It is reasonable to transfuse non–red cell hemostatic blood products based on clinical evidence of bleeding and preferabley guided by point-of-care tests that assess hemostatic function in a timely and accurate manner. (Level of evidence C)**

Class IIb

1. **It is not unreasonable 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)**

Class III

1. **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)**

Objective evidence to support transfusion decisions is incompletely developed. The hemoglobin, hematocrit, or platelet count at which red cell or platelet transfusion is administered is often referred to as the "transfusion trigger." While surgeons, anesthesiologists, and critical

care specialists developed a long-standing tradition of transfusion when the hemoglobin falls below 10 g/dL or hematocrit below 30%, this practice no longer appears appropriate since these recommendations were not evidence based. There is little scientific support for relying upon a specific hemoglobin or hematocrit level as a transfusion trigger. Likewise, estimates of blood loss and intravascular blood volume are often inadequate to assess the needs for transfusion. More advanced measurements such as whole body oxygen-carrying capacity, oxygen consumption, oxygen extraction ratios, and oxygen delivery provide more accurate means to estimate the need for red blood cell transfusions [142].

During cardiac operations, cardiopulmonary bypass provides oxygenation and systemic perfusion in a nonphysiologic manner. Utilizing systemic heparinization, hemodilution and nonpulsatile blood flow in addition to hypothermia, creates a number of physiologic consequences that affect systemic physiology and blood formed elements [143]. With respect to blood transfusion requirements, the use of balanced physiologic solutions as a pump prime, leads to normovolemic hemodilution during cardiopulmonary bypass. The putative advantages of hemodilution during bypass include improvements in tissue perfusion by reducing blood viscosity. In spite of reductions in hemoglobin-bound oxygen transport to tissues, adequate oxygen delivery to tissues is well maintained with hematocrits well below baseline physiologic levels. Hemodilution may contribute to perioperative coagulopathy by diluting the concentration of coagulation factors and platelets. Anemia at the conclusion of cardiopulmonary bypass may theoretically be detrimental to the recovering myocardium in the context of coronary revascularization [144]. However, one study performed in patients immediately after CPB showed no change in myocardial lactate extraction or production even with elective hemodilution to hemoglobin of 5.0 g/dL [145]. Studies done in the early 1980s suggest that hemodilution to hemoglobin of 5.0 g/dL provides adequate oxygen delivery during CPB, but these studies need confirmation in patients with compromised ventricular function and using modern perfusion techniques [146, 147].

The physiologic threshold at which oxygen consumption starts to decrease because of insufficient oxygen delivery in humans is a hemoglobin level of 3 to 4 g/dL, an oxygen extraction ratio of 0.44, a mixed venous oxygen of 34 mm Hg, and a mixed venous oxygen saturation of 56% [148]. Of interest, the lowest limit of critical oxygen delivery of 333 mL O_2/min/m^2, below which oxygen delivery suffers, is the same for all mammalian species [149]. In well-controlled euvolemic hemodilution studies, whole body shift to anaerobic metabolism (ie, falling below critical oxygen delivery threshold) might be the absolute indicator for transfusion. In the context of coronary artery disease, moderate hemodilution during clinical cardiopulmonary bypass is well tolerated by cardiac patients [146]. However, the coronary artery blood flow reserve and oxygen extraction may be exceeded by extreme hemodilution to less than 6 g/dL [150]. Weisel and

colleagues [148] found that patients at risk for perioperative ischemia, presumably most patients having cardiac procedures, showed a delay in myocardial metabolic recovery with substantial hemodilution when postoperative hemoglobin levels fell below 6.0 g/dL. However, transfusion of banked blood was not controlled for in this study. Increases in cardiac output, oxygen extraction ratio, and red cell transit time in capillaries are the primary compensatory mechanisms for reduced oxygen carrying capacity. Patients with compromised ventricular function may not be able to increase cardiac output. There are few data for cardiac surgery patients to address critical end-organ oxygen delivery and utilization in the diseased state, although there are studies that report that tissue oxygenation is maintained in healthy, normovolemic persons with a hemoglobin of 6 to 7 g/dL and hematocrits of 15% to 20% [151, 152]. Fang and colleagues [153] could not find an increased mortality rate among cardiac surgical patients until the perioperative hemoglobin was 5.0 or less. Observational studies provide general guidelines to guide practice, although there are a number of clinical series that provide conflicting data, particularly in specialized patient populations such as the Jehovah's Witness patients.

The original report by Ott and Cooley [154] of cardiac surgery in Jehovah's Witness children demonstrated that such high-risk surgery was possible with a mortality rate of 9.4%. This report helped to define the standards for open heart surgery in this group of patients. In reviews of published series between 1983 and 1990 involving 1,404 operations on Jehovah's Witnesses, anemia and lack of transfusion influenced operative mortality for only 20 patients (1.4%) [155]. A synopsis of 61 reports of 4,722 Jehovah's Witnesses identified 23 deaths due to anemia, all but 2 of which were patients with hemoglobin concentrations less than 5 g/dL [156]. Based upon these reports, major cardiovascular procedures including coronary bypass surgery, are performed safely in Jehovah's Witness patients; and these reports provide level B and C evidence that acute and chronic anemia can be tolerated in certain clinical situations.

Because of the lack of high-level evidence to guide transfusion decisions, recommendations rely on expert opinions. In 1988, the National Institutes of Health convened a consensus conference and published recommendations for blood transfusion, platelet therapy, and administration of fresh frozen plasma [157]. Through these activities and a number of other consensus conferences by the American Association of Blood Banks and the American College of Physicians in the early 1990s, recommendations regarding blood utilization and transfusion practices provided significant focus and attention on this issue [158, 159]. In 1990, the Transfusion Practices Committee of the American Association of Blood Banks issued guidelines for transfusion of patients undergoing coronary artery bypass surgery [160]. In 1994, the ASA convened a task force on blood component therapy to develop evidence-based guidelines on the proper indication for perioperative and peripartum administration of red blood

cells, platelets, fresh frozen plasma, and cryoprecipitate [161]. This task force reviewed a total of 1,417 articles, of which 160 articles were considered relevant. Published evidence was considered relevant if it addressed the perioperative or peripartum use of the blood components and measured effectiveness in terms of clinical outcomes. Identifying the primary objective of red blood cell transfusion as the improvement of inadequate oxygen delivery, the task force identified two assumptions as the principles upon which decisions to transfuse patients should be based: (1) surgical patients experience adverse outcomes as a result of diminished oxygen carrying capacity, and (2) red blood cell transfusions, by enhancing oxygen-carrying capacity, can prevent adverse outcomes.

After separating the effects of hypovolemia and anemia related to blood loss in this literature, it appears that the absolute lowest threshold for hematocrit or anemia in patients can not be established; however, hemoglobin concentrations as low as 7 g/dL were found to be adequate to provide tissue oxygenation in normal, healthy, euvolemic persons. The NIH Consensus Conference concluded that the evidence did not support the use of a single criterion for transfusion such as a transfusion trigger of 10 g/dL [157]. The summation of consensus recommendations is shown in Table 3.

c) Indications for Transfusion on Cardiopulmonary Bypass

Class IIa

1. **During cardiopulmonary bypass with moderate hypothermia, transfusion of red cells for a hemoglobin of 6 g/dL or less is reasonable except in patients at risk for decreased cerebral oxygen delivery (ie, history of cerebrovascular accident, diabetes mellitus, cerebrovascular disease, carotid stenosis), in which case, higher hemoglobin levels may be justified. (Level of evidence C)**
2. **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 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$_2$, electrocardiographic or echocardiographic evidence of myocardial ischemia, and so forth). (Level of evidence C)**

Class IIb

1. **For patients on CPB with risk for critical end-organ ischemia/injury, it is not unreasonable to keep the hemoglobin level at 7 g/dL or more. (Level of evidence C)**

Much has been written regarding the need for improved transfusion indicators in cardiac surgery, particularly during cardiopulmonary bypass [41]. Many reports have tied the decision to transfuse blood components (or the lowest hematocrit on bypass) to postoperative outcome as a means to either confirm the benefits of blood conservation or identify predictors of poor outcome [162, 163]. Among these reports, a number of prospective single-center and multi-center reports offer insight to the management of hemodilutional anemia on cardiopulmonary bypass. In 1997, Fang and colleagues [153] reported the results of a single institution in 2,738 coronary artery bypass graft operations, concluding that after accounting for differences in patient and disease characteristics, a lowest hematocrit value of less than or equal to 14% for low-risk patients and a value of less than or equal to 17% for high-risk patients was an independent risk factor for mortality. In a comprehensive database study from the Northern New England Cardiovascular Disease Study Group, the authors reported that of 6,980 consecutive patients who underwent coronary artery bypass at six medical centers in Maine, New Hampshire, and Vermont and at the Beth Israel Deaconess Hospital in Boston between 1996 and 1998, those whose hematocrit while on cardiopulmonary bypass was allowed to fall below 19% had higher in hospital mortality rates, higher intraoperative use of balloon support, and more frequent return to cardiopulmonary bypass after initial attempts at separation [164]. Women and patients with small body surface area and patients who were anemic before operation were most likely to be severely anemic on cardiopulmonary bypass. Of note, neither of these studies examined transfusion, the usual physician response to low hematocrit, as a covariate or possible cause of the increased mortality.

Several reports suggest worse outcome associated with anemia during CPB. In a recent report evaluating low hematocrit during cardiopulmonary bypass, Karkouti and coworkers [165] evaluated the relationship between nadir hematocrit during cardiopulmonary bypass and perioperative stroke while adjusting for variables known to have an association with stroke and anemia. In prospectively evaluated patients (10,949 consecutive patients) who underwent coronary artery bypass with extracorporeal circulation from 1999 to 2004, nadir hematocrit during cardiopulmonary bypass was an independent predictor of perioperative stroke. After controlling for confounding variables, each percent decrease in hematocrit was associated with a 10% increase in the odds of suffering perioperative stroke. The authors concluded that there is an independent direct association between degree of hemodilution during cardiopulmonary bypass and a risk of stroke.

In a more recent review of the effects of low hematocrit during cardiopulmonary bypass, Habib and coworkers [166] reported a retrospective analysis of operative results and resource utilization in 5,000 consecutive cardiac operations with cardiopulmonary bypass. Stroke, myocardial infarction, low cardiac output, cardiac arrest, renal failure, prolonged ventilation, pulmonary edema, reoperation due to bleeding, sepsis, and multiorgan failure were all significantly increased as lowest hematocrit

value decreased below 22%. Consequently, hospital stays, operative costs, and operative deaths were also significantly greater as a function of hemodilution severity. Long-term survival is improved among patients with higher hematocrits on CPB, suggesting that increased hemodilution severity during CPB is associated with worse perioperative outcomes. Like the reports by Fang and coworkers, Habib and associates did not review the effects of transfusion on outcome in their particular study. Two reports [167, 168] examined large databases to evaluate the effects of anemia on renal function during cardiac procedures. There was an association between lowest hematocrit on CPB and the increased incidence of postoperative renal dysfunction. However, the use of transfusion to treat low hemoglobin or to prevent hemodilutional anemia on bypass multiplied the risks of renal dysfunction twofold to 3.5-fold. Because of these findings, some authors suggest that transfusion of blood products worsens outcomes during CPB [140], but transfusion may just be a marker of disease severity, not a cause of poor outcome. More prospective randomized studies are required to amplify the relationship between blood transfusion and poor outcome after CPB.

Because of the possible association of blood transfusion on CPB with worse outcomes, several investigators evaluated this possibility with observational studies. Surgenor and associates [169] showed that although hemodilutional anemia increases the risk of low-output failure after cardiac procedures, an additional risk-adjusted increase of 27% occurs with the transfusion of 1 to 2 units of packed red blood cells regardless of nadir hematocrit. Intraoperative packed red blood cells transfusion during CABG surgery seems to increase the risk of postoperative low-output heart failure. Engoren and coworkers [170] studied 1,915 patients who underwent first-time isolated coronary artery bypass operations between 1994 and 1997 and found that 649 of the study patients (34%) received a transfusion during their hospitalization. Transfused patients were older, smaller, more likely to be female, and had more comorbidity. The transfused patients also had twice the 5-year mortality (15% versus 7%) of nontransfused patients. After correction for comorbidities and other factors, transfusion was still associated with a 70% increase in mortality. By multivariate analysis, transfusion, peripheral vascular disease, chronic obstructive pulmonary disease, New York Heart Association cardiac functional class IV, and age were significant predictors of long-term mortality. The authors concluded that blood transfusions during or after coronary bypass operations are associated with increased long-term morbidity and mortality. Stroke and death were increased in association with the utilization of platelet transfusions in a study by Spiess and associates [167]. However, a more recent study by Karkouti and coworkers [171] did not find an excess morbidity or mortality in CABG patients who received platelet transfusions. Patients who have lower hematocrits bleed more and otherwise receive more transfusions including platelet transfusions. In a review of more than 15,000 patients undergoing CPB procedures at the Cleveland Clinic, a

strong association was demonstrated between the use of transfusions and postoperative infections [168].

All the data reviewed above are derived from observational studies and therefore only document associations, not cause and effect. Anemia may well drive a number of physiologic responses as well as physician behaviors (ie, transfusion). It is therefore unclear at this time how important any level of anemia is in creating organ failure or long-term adverse outcomes. Further, it is uncertain what role blood transfusion plays in this complex process. For these reasons, blood transfusions should be administered with caution while adhering to guideline recommendations whenever possible.

d) Postoperative Indications for Transfusion
Class IIa

1. **For patients after cardiac operations with hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable and can be life-saving. Transfusion of red cells is reasonable in most postoperative patients with hemoglobin level of 7 g/dL or less, but no high-level evidence supports this recommendation. (Level of evidence C)**
2. **It is reasonable to transfuse non–red 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)**

Decisions about transfusion after operation in ICU patients are complex. It is obvious that the patient's clinical situation and disease status are important factors in determining the need and indication for transfusion in patients undergoing coronary artery bypass surgery. The patient's volume status, pulmonary and cardiac status, cerebrovascular status, the chronicity of anemia, the patient's symptoms, the potential for blood loss, and the extent of surgery and risk of rebleeding all factor into these decisions. Clinical indicators of hypovolemia and its secondary physiologic effects include tachycardia, hypotension, and oliguria. Physiologic indicators of significant impairments of the oxygen supply and demand ratios include mixed venous oxygen saturation (SVO_2) less than 55%, or mixed venous oxygen tension less than 30 mm Hg.

Data to support postoperative transfusion decisions in cardiothoracic practices are sparse. Utilizing clinical judgment in the decision-making process, many clinicians assume that anemia increases the risk of myocardial ischemia after CABG operations, although the previously reviewed experience with Jehovah's Witness patients and other clinical reports offers a contrary opinion [155, 172]. Clinical indicators for postoperative transfusion in coronary artery bypass graft patients taking into account their clinical and disease status were proposed in 1990, and updated in 1996, to provide guidance with respect to indications for transfusion [173, 174]. In the absence of prospective randomized data, these expert recommendations provide a foundation upon which transfusion practices are based and still appear to be

generally applicable to modern cardiothoracic practice (Table 3).

More recent assessments of the impact of transfusion therapies are available. In a retrospective data analysis, Hébert and associates [175] found that patients with cardiac disease admitted to the critical care unit had a significantly higher risk of death with lower hemoglobin values. To further elucidate the potential impact of transfusions on mortality in critically ill patients admitted to a general ICU, the same investigators conducted a prospective, randomized, controlled trial [176] to determine the outcome of a transfusion protocol that maintained hemoglobin level at 7 to 9 g/dL (strict protocol) or at 10 g/dL or more (liberal protocol). They reported that there was no overall difference in mortality between the two groups and that a restrictive protocol was at least as effective and possibly superior to the liberal transfusion protocol. In a subset of patients who had known coronary artery disease, mortality was not different based upon transfusion behavior [177].

In a report from the Multicenter Study of Perioperative Ischemia Research Group, Spiess and coworkers [178] reported that the risk of postoperative myocardial infarction was highest in CABG patients with hematocrit greater than 34% and with more severe left ventricular dysfunction, questioning the rationale for adhering to arbitrary transfusion thresholds in cardiac patients.

Based upon nonrandomized observational studies, descriptive case series, a few prospective randomized clinical trials, and expert panel opinions, consensus suggests that red blood cell transfusion to improve oxygen transport when a hemoglobin level is greater than 10 g/dL is almost never of benefit. The NIH Consensus Conference and the practice guidelines of the ASA concluded that patients with hemoglobin levels greater than 10 g/dL did not require blood, whereas most patients with hemoglobin levels less than 7 g/dL benefit from transfusion [157, 161]. In a recent prospective randomized trial of transfusion of patients after CABG, in-dwelling tissue oxygen probes measured the effect of transfusion with 1 or 2 units of red blood cells [179]. Transfusion did not improve oxygen delivery to tissues, but increasing FiO_2 from 50% to 100% did improve tissue oxygen delivery. Other animal work confirmed this finding [180, 181]. Such work in hemorrhagic rat models did show that vital signs (arterial pressure, central venous pressure) and blood gases (systemic arterial and mixed venous) improved by transfusion of banked blood. With standard critical monitoring, transfusion seems to improve physiologic variables (blood pressure, arterial blood gases, mixed venous blood gases), but the tissue oxygen delivery may actually be reduced by typical banked blood [181]. Much more work needs to be done before the physiologic benefit of blood transfusion is determined. Only then can realistic and evidence-based transfusion triggers be established.

5) Interventions to Limit Blood Transfusion

a) Pharmacologic Agents

I) HEMOSTATIC DRUGS WITH ANTIFIBRINOLYTIC PROPERTIES

Class I

1. **High-dose aprotinin is indicated to reduce the number of patients requiring blood transfusion, to reduce total blood loss, and to limit reexploration in high-risk patients undergoing cardiac operations. Benefits of use should be balanced against the increased risk of renal dysfunction. (Level of evidence A)**

2. **Low-dose aprotinin is indicated to reduce the number of patients requiring blood transfusion and to reduce the total blood loss in patients having cardiac procedures. (Level of evidence A)**

3. **Lysine analogues like epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) are indicated to reduce the number of patients who require blood transfusion, and to reduce total blood loss after cardiac operations. These agents are slightly less potent blood-sparing drugs and the safety profile of these drugs is less well studied compared with aprotinin. (Level of evidence A)**

Three drugs that play a role in perioperative blood conservation and that limit fibrinolysis are in clinical use. Epsilon-aminocaproic acid (EACA [Amicar; Xanodyne Pharmaceuticals, Newport, KY]) inhibits fibrinolysis by the inhibition of plasminogen inhibitors and to a lesser degree through antiplasmin activity. Tranexamic acid (TXA [Cyklokapron; Pharmacia & Upjohn, Somerset County, NJ]) is similar in action to epsilon-aminocaproic acid but it is approximately 10 times more potent. These two drugs are classified as lysine analogues because they inhibit plasminogen by binding to the lysine binding sites on the plasminogen molecule. Aprotinin (Trasylol; Bayer Pharmaceuticals, West Haven, CT) is a bovine protein that inhibits proteases with active serine residues, especially plasmin, resulting in the attenuation of inflammatory responses, fibrinolysis, and thrombin generation. Aprotinin and the lysine analogues have very different modes and scope of action but ultimately inhibit fibrinolysis by limiting the action of plasmin.

Since the early 1990s, antifibironlytic therapies have been widely adopted for cardiac surgery. However with widespread adoption, there is much concern regarding the saffety and efficacy of these drugs (http://www.fda.gov/cder/drug/advisory/aprotinin.htm) [182, 183]. For this reason, the risks and benefits (ischemic complications versus decreased blood loss and transfusion) of these agents must be weighed and continually evaluated. Therefore, guideline recommendations must not only summarize the evidence for the use of the natural serine protease inhibitor aprotinin, and of the lysine analogues, but must also identify safety concerns of these agents.

Heightened awareness of using drugs for blood conservation in cardiac operations surfaced in the late 1980s with the observation that aprotinin, given to humans in a far higher dose than previously used, was able to reduce bleeding to the point where the majority of patients did not require transfusions. That was seen even in patients

having repeat surgery through a previous sternotomy [184], a patient population regarded at that time as being at a very high risk for transfusion. Subsequently, a large number of studies investigated the effects of various dose regimens of aprotinin, TXA, and EACA on postoperative bleeding and blood transfusion. Arguably, no other blood conservation interventions have been as well studied and reported in the literature as have the antifibrinolytic drugs, especially aprotinin. For example, at least 49 randomized, controlled trials encompassing more than 4,000 subjects were identified that addressed the efficacy of aprotinin in limiting the number of patients transfused during cardiac procedures.

A search of MEDLINE, EMBASE, and CINHAL databases for the period January 1980 to July 2006 with the key words aprotinin, Trasylol, Iniprol, Midran, Cyclokapron, tranexamic acid, Amicar, epsilon-aminocaproic acid, and EACA in combination with coronary-artery-bypass, myocardial revascularization, aortocoronary bypass, valve, aortic or mitral surgery found more than 600 studies investigating the effect of lysine analogues and aprotinin on postoperative bleeding. There are roughly three times as many articles published that address the blood conservation properties of aprotinin than of the lysine analogues. At least four meta-analyses address the relative benefits of the three antifibrinolytic drugs in limiting blood loss and blood transfusion after cardiac procedures [185–188].

More than 70 trials compared aprotinin and placebo in patients having cardiac procedures using CPB. Of these 70 trials, 28 were randomized studies with adequate information to compare outcomes. Twenty-eight evaluable studies compared high-dose aprotinin to control subjects in more than 4,000 patients having cardiac procedures. Meta-analysis showed a highly significant reduction in blood transfusion in aprotinin-treated patients having CABG alone (Fig 2). Similar results were found in five studies [184, 189–192] of patients having redo CABG operations and in eight studies [193–200] of patients having valve or valve/CABG operations. The evidence favoring reduced transfusion is somewhat less compelling, but still robust, for lower doses of aprotinin [201–211] or for dosing of aprotinin in the CPB circuit only [201, 204, 207, 212–219]. The amount of blood transfused was studied in 16 trials of patients receiving EACA, and in 35 trials of patients receiving TXA. Similar benefits for the lysine analogues were observed in the number of transfusions and the number of patients transfused. For evaluable studies of the lysine analogues, significant reductions in transfusions were seen in patients having a variety of cardiac procedures using CPB compared with placebo-treated patients [215, 218, 220–226].

Another important indicator of operative blood loss is return to the operating room for control of hemorrhage. This outcome measure is an infrequent occurrence but indicates excessive bleeding. Exploration for postoperative hemorrhage is associated with serious postoperative morbidity, and limiting this complication should improve operative mortality and morbidity [220, 227]. There were 17 high-dose aprotinin studies (14 CABG only and 3
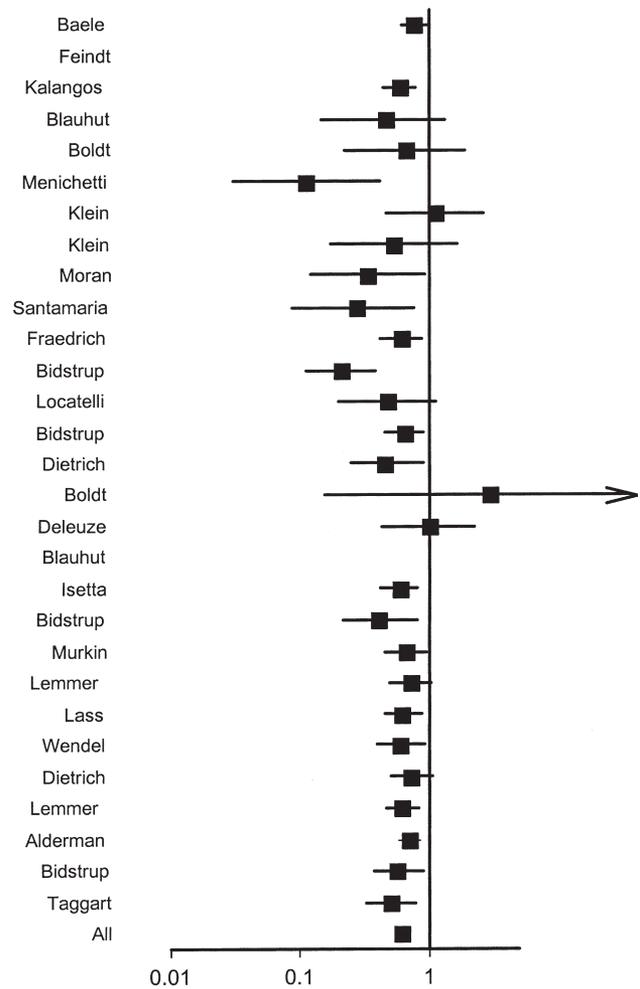

Fig 2. Relative risk ratios with 95% confidence intervals for primary coronary artery bypass graft surgery (CABG) and high-dose aprotinin (840 mg). Forest plot of randomized trials (First authors are at left) comparing blood transfusion in high-dose aprotinin-treated patients versus placebo-treated patients undergoing CABG only (no reoperations included). Studies to the left of midline favor aprotinin therapy. There is a highly significant benefit from aprotinin in reducing the number of patients transfused after CABG.

CABG/valve) and 11 lysine analogue studies (6 CABG only, and 5 CABG/valve) that reported the rate of return to the operating room for postoperative hemorrhage. Table 5 summarizes the available evidence about return to the operating room for postoperative hemorrhage after cardiac procedures. Aprotinin is associated with a significant reduction in the rate of return to the operating room for control of postoperative hemorrhage. No similar benefit in rate of return to the operating room is seen with the lysine analogues.

(1) Meta-analyses of antifibrinolytic drug therapy. Independent randomized controlled trials (RCTs) demonstrate the blood-saving benefits of antifibrinolytic therapies. Although RCTs provided the initial evidence for use of these agents, meta-analyses are used to confirm their efficacy and to assess safety. Four meta-analyses summa-

Table 5. Rates of Return to Operating Room for Postoperative Hemorrhage in Patients Treated With Aprotinin and Tranexamic Acid[a]

	Treatment Reexplore		No Treatment Reexplore			
	Yes	No	Yes	No	RR	CI
Aprotinin	18	1,099	56	1,043	0.316	0.188–0.53
Tranexamic acid	14	354	17	362	0.848	0.429–1.674

[a] Results are pooled from 17 high-dose aprotinin studies and 11 tranexamic acid studies.

CI = confidence interval;   RR = relative risk.

rize the primary efficacy of antifibrinolytic therapies in limiting blood transfusion during cardiac operations [47, 186, 187, 228]. More importantly, these meta-analyses summarize the rare secondary outcomes (mortality, stroke, myocardial infarction, and renal complications) where independent trials lack the statistical power to detect harm or benefit. For example, only one independent randomized trial reported a significant occurrence of renal dysfunction in patients treated with aprotinin [229], whereas a recent meta-analysis and two large observational studies suggest that high-dose aprotinin is associated with an increased incidence of renal dysfunction [182, 183, 230]. Despite the efforts by past RCTs and meta-analyses to evaluate safety data of these agents, questions remain about their safety and efficacy.

The most recent meta-analysis is that of Sedrakyan and coworkers [186]. These authors build on the previous meta-analyses [47, 187, 228] by updating previous trials with more recent RCTs. All of the available meta-analyses analyzed trials, some of which were RCTs, to summarize the primary and secondary outcomes for patients treated with aprotinin, EACA, or TXA during cardiac operations using CPB.

The meta-analysis by Munoz and associates [47], done in 1999, showed that aprotinin and EACA significantly limited postoperative blood transfusion and that EACA was a viable and cost-effective alternative to aprotinin. These authors showed that high-dose aprotinin significantly reduced packed red blood cell transfusion by 72% (0.28%, 0.22% to 0.37%), whereas EACA reduced packed red blood cell transfusion by 68% (0.32%, 0.15% to 0.69%). In addition, Munoz and associates [47], showed that high-dose aprotinin reduced total blood loss by 53%. Low-dose aprotinin and EACA reduced total blood loss by 35%, significantly less than high-dose aprotinin.

In 2001, Henry and associates [187] added current RCTs to those found by Munoz and associates [47] and showed that aprotinin reduced the need for transfusion by 31% (relative risk [RR]: 0.69; 95% confidence interval [95%CI]: 0.63 to 0.76). This was true for pump prime dose, low-dose, and high-dose aprotinin: RR 0.85 (0.73 to 0.99), 0.69 (0.59 to 0.80), and 0.68 (0.62 to 0.75), respectively. Likewise, TXA significantly reduced transfusion by 29%

for all cardiac procedures. However, the evidence for EACA was limited and was not significantly associated with reduced transfusion (RR: 0.48; 95%CI: 0.19 to 1.19) in this meta-analysis.

In 2004, Sedrakyan and associates [186] reported a meta-analysis of patients having isolated CABG that further updated the RCTs that address the efficacy and safety of antifibrinolytic drugs. These authors examined 35 RCTs encompassing 3,879 patients having CABG. They found that aprotinin significantly reduced the need for transfusion by 39% compared with control patients. Aprotinin treatment had no effect on operative mortality, myocardial infarction, or renal failure but did have a beneficial effect on limiting postoperative stroke.

In these meta-analyses, high-dose aprotinin was the only agent shown to reduce the risk of reexploration for any cause (Table 5). Neither TXA nor EACA significantly reduced the reexploration rate. In general, these meta-analyses found that none of the agents reduced mortality, myocardial infarction, stroke, thrombosis, or renal dysfunction. Two notable exceptions were the study by Sedrakyan and associates [186] that found a significant reduction in stroke for isolated CABG patients treated with aprotinin, and the study by Munoz and associates [47] that found a trend toward increased renal dysfunction in aprotinin-treated patients. Recently, Brown and associates [230] updated the meta-analysis of Munoz and associates [47] and found an excess of renal dysfunction, but not renal failure, in aprotinin-treated patients. Brown and coworkers [230] found that 5 of every 100 cardiac patients treated with aprotinin may have an increase above control of postoperative serum creatinine of more than 0.5 mg/dL during the early postoperative period. This increase in serum creatinine did not seem to be associated with the development of renal failure. These findings support the earlier trial of D'Ambra and coworkers [229] and the observational studies of Mangano and associates [182] and Karkouti and associates [183].

(2) Head-to-head comparisons of antifibrinolytic drugs. A peculiarity of studies that compare antifibrinolytic agents to placebo is that there is a wide variation in the transfusion rates of control patients. For example, in one recent study of 100 patients randomly assigned to aprotinin or placebo, 79% of control patients received blood products compared with 53% of aprotinin-treated patients [231]. In another study of 75 patients randomly assigned to EACA or placebo, 36% of control patients received blood products compared with 18% of EACA-treated patients [232]. Differences of this sort in the control transfusion rates suggest that these two studies would not be suitable for a meta-analysis. In statistical terms, this implies heterogeneity among the studies. Statistical tests are available to test the hypothesis that the effect sizes among RCTs are equal. If the RCTs used to perform a meta-analysis do not exhibit homogeneity, that suggests a flawed meta-analysis [233]. None of the available meta-analyses that compare antifibrinolytic drugs to placebo report indices of homogeneity of effects size, and that is a shortcoming of these studies. This

shortcoming makes it difficult if not impossible to determine superiority of one antifibrinolytic drug over another. One way to address this shortcoming is to perform meta-analysis on RCTs that compare one antifibrinolytic drug directly to another in head-to-head comparisons.

Unfortunately, the literature is sparse on head-to-head comparisons of aprotinin with EACA or TXA. Fourteen studies, involving 1,057 patients, compared one or more antifibrinolytic drugs to another in head-to-head comparisons among patients having various cardiac procedures [197, 198, 220, 222, 223, 234–243], and only the study of Hardy and associates [220] compared EACA with TXA, while all others compared aprotinin with TXA (9 studies), with EACA (2 studies), or with both (3 studies). In nearly all of the studies that compared EACA with aprotinin, there was a suggestion that aprotinin resulted in less transfusion and fewer numbers of patients transfused than either placebo or EACA [198, 223, 235, 240, 244]. Although the numbers are small, meta-analysis suggests that treatment with high-dose aprotinin is better than any dose of EACA but is equivalent to treatment with TXA (results not shown). Only 2 of 12 studies showed that aprotinin significantly reduced packed red blood cells transfusion compared with TXA [197, 223]. None of the 13 studies that compared aprotinin with TXA or EACA suggested that either of the lysine analogues were better than aprotinin in reducing blood transfusion or in reducing the number of patients transfused. Because of concerns about blinding in these studies, because of wide dose ranges in TXA-treated groups, because of apparent lack of homogeneity, and because of small numbers, making recommendations on the basis of these direct comparisons is not justified.

(3) Safety of antifibrinolytic drugs in cardiac surgery. Two recent observational studies [182, 183] and one meta-analysis [185] suggest that aprotinin may be associated with increased thrombotic risk, especially renal dysfunction, after cardiac procedures. That caused the Food and Drug Administration to issue a safety alert suggesting that aprotinin should be used with caution and only for patients in whom the benefits of the drug outweighs the risks, mostly of renal dysfunction and of hypersensitivity (http://www.fda.gov/cder/drug/advisory/aprotinin.htm). There has always been some concern about the effect of aprotinin on renal function because of its affinity for the proximal renal tubules [245, 246]. D'Ambra and associates [229] observed a significantly higher rate of renal dysfunction in patients undergoing valve surgery who received aprotinin. This dysfunction appeared to be more likely in patients with diabetes mellitus (16% versus 5%), a result supported by Mangano and associates [182]. Kincaid and associates [247] in a retrospective logistic regression analysis of 1,200 patients undergoing CABG found that the combination of angiotensin-converting enzyme inhibitors plus aprotinin administration was associated with an increase rate of acute renal failure (odds ratio 2.9, confidence interval: 1.4 to 5.8) while neither drug alone was associated with this complication. Karkouti and associates [183], in a propensity score matched

retrospective comparison of 898 patients who received either aprotinin or TXA, found that the incidence of renal dysfunction and dialysis was higher among those receiving aprotinin (24% versus 17%, $p = 0.01$). It is likely that patient comorbidities and drug-drug interactions involving aprotinin are associated with an excess of renal dysfunction, suggesting that aprotinin should be used with caution in patients with certain comorbidities such as diabetes or with preexisting renal dysfunction. Patients who receive certain preoperative medications that have adverse renal effects such as angiotensin-converting enzyme inhibitors may also be at risk for interactions with aprotinin. Until further information becomes available, the enhanced blood-sparing benefits of aprotinin should be applied with caution in certain patients.

Other safety issues affect the administration of aprotinin for blood conservation during cardiac procedures. Because aprotinin is a bovine protein, hypersensitivity reactions upon administration to humans are a possibility. Evidence suggests that a significant hypersensitivity reaction (50% of which are anaphylaxis) occurs in less than 0.1% of patients who have an initial exposure to the high-dose regimen of aprotinin during cardiac operations. This rate rises to 5% if patients have a reexposure to aprotinin within 6 months of initial dosing [248, 249]. The hypersensitivity reaction to initial exposure of aprotinin is rare and is not greater than for other nonhuman protein drug exposures. In some formulations of fibrin glue, aprotinin is used to prevent fibrinolysis. That can be an unrecognized cause of antibody formation and rarely leads to anaphylactic reactions upon early reexposure.

Review of the safety issues of the antifibrinolytic drugs highlights an important point, namely most efficacy trials are neither designed nor powered to uncover low frequency drug-related morbidity like renal failure, coronary graft occlusion, or other infrequent morbidities. Even trials designed to evaluate a specific drug-related morbidity may suffer from problems with statistical power. Few data exist to support the safety of EACA and TXA, but no evidence suggests that excess complications are associated with use of these antifibrinolytic agents. Phase IV studies are important to evaluate drug safety after regulatory approval [250, 251]. Additional phase III trials are needed to assess the safety of lysine analogues, especially with regard to renal dysfunction. There is a concerning lack of reporting of renal complications for EACA, TXA, and low-dose aprotinin. Likewise, more high-quality large phase III trials are needed to examine head-to-head comparisons of antifibrinolytic agents including high- and low-dose aprotinin, EACA, and TXA.

Meta-analyses are effective at summarizing the treatment effects of reported outcomes of interest, but are limited by the trial design and bias in recruitment of patients. The meta-analyses reported to date do not support the suggestions of Mangano and associates [182] that aprotinin is associated with increased risk of mortality, stroke, myocardial infarction, or dialysis-dependent renal failure. However, one meta-analysis supports the suggestions of these authors that there is an increased risk of renal dysfunction, but not renal failure, associated

with the use of high-dose aprotinin during cardiac procedures [230]. Until more information is available, aprotinin should be used with caution.

In summary, high- and low-dose aprotinin, EACA, and TXA are all effective at significantly reducing total blood loss and the need for packed red blood cells transfusion. Only high-dose aprotinin has been shown to significantly reduce the risk for reexploration. None of the agents reduces mortality, myocardial infarction, thrombosis, or renal failure or renal dysfunction. Among only the isolated CABG patients, a significant reduction in stroke was observed in aprotinin treated patients. High-dose aprotinin has been associated with increased risk of renal dysfunction, but not renal failure. There is limited head-to-head evidence to support the use of one agent over the other.

II) ERYTHROPOIETIN

Class IIa

1. Recombinant human erythropoietin (EPO) is reasonable to restore red blood cell volume in patients undergoing autologous preoperative blood donation before cardiac procedures. However, no large-scale safety studies for use of this agent in cardiac surgical patients have been performed. Available evidence suggests an acceptable safety profile. (Level of evidence A)
2. Recombinant human erythropoietin is a reasonable alternative for anemic low-risk elective patients (hemoglobin ≤ 13 g/dL) before cardiac procedures providing that EPO is given in conjunction with iron therapy several days or more before operation. (Level of evidence B)

Class IIb

1. It is not unreasonable to use preoperative EPO, given at least a few days before operation, to increase red cell mass in elective patients who are at risk for postoperative anemia and depressed endogenous EPO production. (Level of evidence C)

Erythropoietin (EPO) is an endogenous glycoprotein hormone that stimulates red blood cell production in response to hypoxia and anemia. Endogenous EPO is produced by the kidney and its production is significantly diminished in patients without adequate renal function. Recombinant human EPO was developed in the mid 1980s and is commercially available in several forms. Erythropoietin combined with oral iron therapy is indicated to treat anemia (hemoglobin levels < 13 g/dL) in renal failure, associated with chemotherapy or HIV, and when given preoperatively, to reduce transfusions in a wide range of operations [252].

Abundant evidence, including four meta-analyses [253–256], exists to justify the preoperative administration of EPO to reduce preoperative anemia especially in patients having autologous blood donation [257–260], and in children [261, 262]. Erythropoietin appears to be safe and effective for the improvement of preoperative ane-

mia, with the main side effect being hypertension. Adequate iron supplementation is required in conjunction with EPO. A typical preoperative regimen of EPO is costly, and uncertainty exists about the cost effectiveness of EPO for patients undergoing autologous blood donation before cardiac procedures.

Evidence supporting the preoperative use of EPO in anemic patients (hemoglobin ≤ 13 g/dL) without autologous predonation is less compelling, but still supportive. Most of the literature in support of using EPO to reduce preoperative anemia is anecdotal and relates successful case reports in a handful of patients, especially in Jehovah's Witnesses [253, 263–269]. Since preoperative anemia increases operative mortality and morbidity in cardiac procedures [270], EPO can be expected to reduce this by augmenting red cell mass in anemic patients treated with iron, if given more than 1 week before operation. This recommendation is based on limited evidence and logical consensus. No large-scale safety studies exist in patients having cardiac procedures, and therefore if one pursues such use, it must be realized that this is "off-label" and not studied. For patients with unstable angina or even stable angina, there is limited support to pursue the use of preoperative EPO because safety data are lacking. Preoperative interventions using EPO seem justified for elective patients with diminished blood volume 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. Logic supports the addition of EPO to patients expected to have a large blood loss during operation or who are anemic preoperatively. Beta-blockers suppress endogenous EPO production [271]. Cytokines stimulated by the inflammatory response associated with CPB limit production of EPO [272]. Perioperative renal ischemia may limit the production of EPO. Likewise, careful perioperative management may improve tissue oxygen delivery, and suppress endogenous EPO production despite postoperative anemia. All of these factors support the addition of preoperative (a few days before operation) administration of EPO, despite the lack of evidence, to treat reduced red blood cell volume in selected patients.

III) DDAVP AND RECOMBINANT FACTOR VIIA

Class IIb

1. Use of desmopressin acetate (DDAVP) is not unreasonable 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)
2. Use of recombinant factor VIIa concentrate is not unreasonable for the management of intractable non-surgical bleeding that is unresponsive to routine he-

mostatic therapy after cardiac procedures using CPB. (Level of evidence B)

Class III

1. **Routine prophylactic use of DDAVP is not recommended to reduce bleeding or blood transfusion after cardiac operations using CPB. (Level of evidence A)**

Desmopressin acetate (DDAVP [1-deamino-8-d-arginine vasopressin]) is a drug approved for replacement therapy in patients with pituitary hypofunction. It releases endogenous factor VIII precursors, von Willebrand factor, and tissue-type plasminogen activator from vascular endothelium. The endogenous stores of factor VIII precursor released by DDAVP are not readily replaced and require as long as 2 weeks to replenish. Numerous studies, including three meta-analyses, addressed the efficacy of DDAVP in limiting bleeding after cardiac operations using CPB [188, 228, 273–288]. When administered prophylactically, DDAVP does not reduce bleeding after cardiac procedures. This agent is not helpful intraoperatively for prophylactic purposes to reduce bleeding after cardiac procedures. However, observational and prospective, randomized data suggest that certain patient subgroups may benefit from off-label use of this agent. Desmopressin acetate might be considered preoperatively in some patients with acquired or inherited defects in primary hemostasis detected by abnormal point-of-care tests that measure platelet function (eg, PFA-100) [276, 289]. A vast majority ($> 90\%$) of patients who are identified preoperatively having either acquired or inherited (ie, von Willebrand's disease) defects in primary hemostasis by PFA-100 testing benefit from use of DDAVP. Koscielny and coworkers [290] found that DDAVP reversed more than 90% of PFA-100 abnormalities of acquired or inherited defects in primary hemostasis if given before operation. Reversal of these primary hemostatic abnormalities was associated with significant decreases in bleeding and blood transfusion [290].

Evidence exists that an important component of postoperative hemostasis is related to the factor VII/tissue factor extrinsic pathway of thrombin and fibrin generation [291, 292]. Hence, it is not surprising that when recombinant, activated factor VII (r-FVIIa) became available commercially, it was quickly used for intractable bleeding during and after cardiac procedures using CPB. Almost all of the experience with this potent hemostatic drug is anecdotal [293–304]. However, there seems to be a very consistent benefit from this drug in limiting life-threatening bleeding, especially when there is a marginal response to routine hemostatic therapy, including patients on extracorporeal membrane oxygenation [295], and children undergoing high-risk complex cardiac procedures [300]. Clinicians realized the uncontrolled nature of these observations and a randomized trial is under way [305]. Others have issued cautionary reports of using this agent off-label with respect to a propensity toward thrombotic complications especially in patients at high risk [306–309]. Patients undergoing routine cardiac surgery may be at a substantially higher risk for development of thrombotic complications with this agent because of elevated systemic levels of tissue factor and thrombin that occur during CPB [308]. These concerns are mirrored by the FDA's recent mandate to include a warning on the package insert of this agent. Until more evidence is available about the risks and benefits of this drug, it can only be recommended as a rescue therapy for severe intractable bleeding without an identifiable surgical source that is unresponsive to routine approaches after cardiac procedures using CPB.

b) Devices That Aid Blood Conservation

I) VENTILATOR-ASSISTED BLOOD CONSERVATION—POSITIVE END-EXPIRATORY PRESSURE

Class IIb

1. **A trial of therapeutic positive end-expiratory pressure (PEEP) to reduce excessive postoperative bleeding is not unreasonable. (Level of evidence B)**

Class III

1. **Use of prophylactic PEEP to reduce bleeding postoperatively is not effective. (Level Evidence B)**

Increased end-expiratory airway pressure (PEEP) exerts mechanical pressure on the myocardium and may limit microvascular bleeding after heart surgery. Several reports address this hypothesis. Two uncontrolled studies found that application of escalating doses of PEEP (5, 10, 15, 20 cm H_2O) controlled excessive bleeding (> 200 mL/h) in 15 of 15 and 11 of 15 patients [310, 311]. Conversely, one small RCT in 35 patients who bled more than 180 mL in the first hour after cardiac procedures reported no difference in subsequent bleeding among those who received PEEP at 10 cm H_2O as compared with no PEEP [312]. Four small RCTs (80, 83, 85, and 129 patients undergoing predominantly elective CABG) found no difference in chest drainage or return to the operating room for postoperative hemorrhage when PEEP was applied prophylactically (starting at time of sternal closure [311], on admission to ICU [313, 314], or 1 hour postoperatively [312]). Based on limited evidence, prophylactic PEEP is not useful, but PEEP administered for unusually high chest tube output may be helpful in a few cases. When PEEP is effective, the benefits are usually apparent within an hour. More data are required to assess the risk/benefit relationship of increasing PEEP in the postoperative setting in which cardiac hemodynamics may be compromised.

II) OXYGENATOR TYPES

Class IIb

1. **It is not unreasonable to use open venous reservoir membrane oxygenator systems during cardiopulmonary bypass for reduction in blood utilization and improved safety. (Level of evidence C)**

Several oxygenator types are available for the conduct of CPB, including bubble oxygenators as well as closed and open membrane oxygenators. Excellent summaries of the types of oxygenators are available [315]. A gradual evolution from film oxygenators to bubble oxygenators and ultimately to membrane oxygenators occurred during the last 50 years. Bubble oxygenators require a direct blood-gas interface whereas membrane oxygenators require diffusion of gas through a permeable membrane separating blood and oxygen. Film oxygenators have disappeared from clinical use because of significant technical problems, including large priming volumes and labor intensive setup that limited clinical usefulness.

Bubble oxygenators compare favorably to membrane oxygenators in most comparisons except for bypass runs exceeding 2 hours [316–323]. Initial objections to the routine use of membrane oxygenators included increased cost and setup time. Advantages of membrane oxygenators include elimination of the direct blood-gas interface, separate control of oxygen and carbon dioxide, and elimination of antifoaming agents in the prime. Responses of oxygenator manufacturers reduced the cost premium associated with membrane oxygenators and, simultaneously, benefits of membrane oxygenators appeared in the literature. Advantages found with membrane oxygenators included fewer cerebral emboli [324], better biocompatibility [321, 323], and reduced blood utilization [325, 326]. Without much class I evidence base, membrane oxygenators have mostly replaced bubble oxygenators in modern clinical practice. Driving forces for this preference include decreasing costs of membrane oxygenators, easier setup of perfusion equipment, perceived benefit in complex cases with prolonged CPB times, and improved safety with less chance of massive air embolism. In the event of loss of venous return, large amounts of air can be transported across the oxygenator, but only infrequently into the patient, with membrane oxygenators, whereas bubble oxygenators risk immediate embolization of air into the arterial circuit. That constitutes an important potential safety benefit of membrane oxygenators and consensus may favor membrane oxygenators for this reason.

Membrane oxygenator systems can have either closed or open venous systems. No clear benefit in improved biocompatibility, lower embolic load, or reduced blood transfusion accrues to either open or closed systems. One serious drawback to the closed venous reservoir in membrane oxygenator systems is the handling of air in the venous reservoir. Either a venous air filter or an extra source of venous reservoir is required to remove air in the closed membrane systems [327, 328], This constitutes a potential perfusion difficulty that can be eliminated by using the open membrane oxygenator systems.

III) PERFUSION BLOOD PUMPS

Class IIb

1. All commercially available blood pumps provide acceptable blood conservation during CPB. It is not unreasonable to prefer centrifugal pumps because of perfusion safety features. (Level of evidence B)

A critical component of the heart-lung machine is the blood pump. Current clinical use is about evenly divided between centrifugal and roller pumps. Fundamental differences exist between the two types, with centrifugal pumps being nonocclusive and roller pumps being able to generate unlimited pressure because of occlusion at the roller head. The nonocclusive nature of the centrifugal pumps is one of the positive features of this pump system, especially for long-term support. Because the output of the centrifugal pumps is related to inlet pressure and outlet pressure, small amounts of air in the pump will "deprime" the centrifugal system, and the potential for massive air embolism is very much diminished. The nonocclusive feature of the centrifugal pump is also a potential draw-back as it allows for possible exsanguination of the patient if the perfusionist forgets to clamp the arterial line at the end of perfusion. Suppliers of perfusion pumps are sensitive to the potential for mishaps and include various alarms and safety measures in the manufacture of these devices [329], so much so that perfusion accidents related to the blood pumps during CPB are exceedingly rare.

Perfusion blood pumps do not impact blood transfusion in a significant way. Nine randomized trials compared blood loss in patients perfused with centrifugal pumps versus roller pumps [330–338]. No significant differences in bleeding or blood transfusion were found in patients perfused with roller or centrifugal pumps. There are theoretical advantages in blood conservation seen with centrifugal pumps. These advantages include reduced complement activation and preserved platelet function [339–341]. So far, these theoretical benefits have not translated into consistent reduction in bleeding or blood transfusion after cardiac procedures with centrifugal pumps.

IV) HEPARIN MANAGEMENT DURING CARDIOPULMONARY BYPASS

Class IIb

1. For patients requiring longer CPB times (> 2 to 3 hours), it is not unreasonable to consider maintenance of higher or patient-specific heparin concentrations during CPB to reduce hemostatic system activation, reduce consumption of platelets and coagulation proteins, and reduce blood transfusion. (Level of evidence B)

Anticoagulation is used during cardiac surgery to limit cellular and coagulation factor activation and to prevent overt thrombosis of the extracorporeal circuit. Heparin is routinely used because it is effective, immediately reversible, generally well tolerated, and inexpensive. Unfractionated heparin is a polysaccharide mixture of low and high-molecular-weight fractions (ie, molecules ranging from 1,000 to 50,000 Daltons) that differ functionally. Fractions with minimum chain length of 18 oligosaccharide units and a molecular weight of approximately 4,500 Daltons or higher preferentially inhibit thrombin [342]. Oligosaccharide chain length is important because thrombin inhibition requires simultaneous binding of thrombin and antithrom-

bin III by heparin, which acts as a template. Only one in three unfractionated heparin molecules has the critical pentasaccharide sequence required for binding to antithrombin III [343]. Although binding of heparin to antithrombin III inhibits thrombin and factor Xa [344], this complex also inhibits several other sites in the intrinsic and extrinsic pathways [345, 346].

There is substantial variability of heparin anticoagulant responsiveness, as illustrated by a wide range of heparin dose-response curves in patients undergoing cardiac surgery with CPB [347, 348]. Impaired heparin responsiveness (ie, also termed heparin resistance) is often attributed to antithrombin III deficiency, but significant variability in heparin anticoagulant response may also result from patient differences in heparin binding to endothelial cells [349], white cells [350], platelets [351, 352], or proteins [353] such as vitronectin [354], vWF [355], or histidine-rich glycoprotein [356]. The heparin tissue source (ie, intestinal versus lung, porcine versus bovine), method of preparation, and the molecular weight distribution of heparin used may also contribute to impaired responsiveness [357, 358]. Unfortunately, no currently available tests can help clinicians identify the specific cause of heparin resistance or variable response to heparin.

When compared with no monitoring, heparin/protamine dosing guided by activated clotting time (ACT) did not consistently limit chest tube drainage and transfusion outcomes [359–369]. Of 11 studies, six demonstrated a reduction in chest tube drainage and five showed no difference. Only seven of the studies investigated transfusion outcomes, and five of these showed that ACT-based protocols reduced transfusion requirements. Only two of these 11 studies were prospective [360, 367], and neither involved a randomized, blinded study design, which may limit the accuracy and reliability of the conclusions. Likewise, when compared with either fixed dose [370] or ACT-based dosing [371–374], the impact of heparin concentration monitoring on bleeding and blood conservation varied. Although some authors suggest that excessive bleeding is related to larger doses of bovine heparin during CPB [374, 375], others found no differences in blood loss when either bovine [371, 376] or porcine heparin were used [372, 373, 377, 378].

One important randomized prospective trial evaluated the effect of heparin and protamine administration directed by a point-of-care whole blood hemostasis system (Hepcon; Medtronic Blood Management, Englewood, Colorado) on bleeding and blood transfusion in 254 patients [373, 379]. When compared with an empiric ACT-based dosing regimen for heparin and protamine, the intervention cohort using point-of-care testing received 25% larger total doses of heparin and had 25% smaller protamine-to-heparin ratios. A patient-specific, reference heparin concentration curve was measured in each intervention patient before CPB, and ACT levels during CPB were maintained at 480 s based on the preoperative heparin concentration curve. The protamine dose was calculated from the measured, residual heparin concentration. When compared with control patients, fewer patients in the intervention cohort required platelets (22% versus 34%, $p = 0.03$), fresh frozen plasma (11% versus 31%, $p < 0.001$), and cryoprecipitate (0% versus 5%, $p = 0.01$). Control patients also had 10% longer operative post-CPB closure times ($p = 0.02$), 15% more mediastinal chest tube drainage ($p = 0.05$) in the first 4 postoperative hours, and twice as many control patients required hemostatic blood product transfusions (17% versus 33%, $p = 0.005$). This study suggests that maintenance of heparin concentrations that more effectively inactivate thrombin may preserve hemostasis during prolonged CPB. The fact that generation of thrombin degradation products [374, 380] and inhibition of clot-bound thrombin [381] are inversely related to heparin concentration supports this hypothesis. Higher, stable heparin concentrations during CPB can also preserve platelet function during prolonged CPB. In a recent trial, less platelet activation (ie, lower platelet factor 4 and BTG levels) was demonstrated in patients who received larger heparin doses [376]. Higher doses of heparin limited blood transfusion in two clinical studies that evaluated blood conservation in high-risk patients. The first study evaluated 31 patients requiring repeat or combined cardiac procedures (ie, coronary revascularization plus valve repair/replacement) [377]. Maintenance of higher heparin concentrations better preserved consumable antithrombin III and factors I, V, and VIII, most likely related to better suppression of thrombin (65% reduction in FPA levels) and fibrinolytic activity (50% reduction in D-dimers). A second study demonstrated that larger heparin doses better suppress thrombin (ie, lower TAT complexes) and fibrinolytic activity (ie, lower D-dimers) in patients undergoing deep hypothermic circulatory arrest than do lower doses of heparin, especially when aprotinin is used as a hemostatic agent [376]. Considering all available evidence, it is reasonable to use higher doses of heparin with point-of-care patient-specific testing to better inhibit thrombin generation and to limit blood transfusion in high-risk patients likely to require prolonged CPB.

V)   PROTAMINE DOSING

Class IIb

1. **It is not unreasonable to 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-to-heparin ratio at the end of CPB to reduce bleeding and blood transfusion requirements. (Level of evidence B)**

Monitoring protocols can markedly influence protamine doses used to neutralize heparin [370, 378, 382–387]. Two recent studies compared the use of a new point-of-care hemostasis system (RxDx System; International Technidyne, Edison, New Jersey) to standard ACT-based empiric regimens in adult patients undergoing cardiac surgical procedures [378, 387]. The RxDx

system estimates patient-specific anticoagulant response to heparin (heparin response titration), determines celite ACT values, and calculates protamine dose by using ACT-based approximations of heparin concentration (eg, protamine response test). When compared with control patients whose anticoagulation and reversal were based on empiric regimens, Jobes and associates [378] demonstrated that RxDx produced a 50% reduction in the protamine dose ($p < 0.01$), which resulted in 50% less chest tube drainage ($p = 0.01$) and 80% fewer transfusions ($p = 0.02$) in the first 24 postoperative hours. In contrast, Shore-Lesserson and associates [387] did not observe a reduction in blood loss and transfusion requirements nor was the protamine dose substantially decreased by use of the RxDx system. Of eight published studies that specifically evaluated the clinical impact of reducing protamine dose, four showed either reduced blood loss or transfusion requirements [378, 382–384], and four did not [370, 385–387]. The discrepancy in outcomes between these studies probably relates to differences in the relative extent of reduction in protamine dose and the overall protamine-to-heparin ratio in the intervention cohort. Thus, in the four studies that demonstrated a favorable difference in outcome, better bleeding or transfusion outcomes occurred when the reduction in protamine dose was approximately 50% or greater and when the protamine-to-heparin ratio was less than 1 [378, 382–384]. The four negative studies had either smaller reductions in protamine dose (27% to 38%) or protamine-to-heparin ratios consistently greater than 1, or both. It may be reasonable to 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-to-heparin ratio at the end of CPB, but more evidence is necessary before a higher class recommendation (class I or IIa) can be made.

VI)   HEPARIN-BONDED CIRCUITS AND LOW-DOSE HEPARIN FOR CPB

Class IIb

1. **Heparin-coated bypass circuits (either the oxygenator alone or the entire circuit) are not unreasonable for blood conservation in cardiac operations. (Level of evidence B)**
2. **Low doses of systemic heparinization (ACT approximately 300 s) are not unreasonable for blood conservation during CPB, but the possibility of under-heparinization and other safety concerns have not been well studied. (Level of evidence B)**

Activation of platelets and the blood coagulation cascade occurs from interaction of the circulating blood with the synthetic surfaces of the heart-lung machine. Coating of the oxygenator and of the bypass circuit minimizes this activation process and ultimately may improve blood conservation after cardiac procedures. The most common synthetic coating used in bypass circuits is heparin. Several commercial products are available in the United States and Europe

employing different means of binding the heparin to the synthetic surfaces. Heparin coating of the entire bypass circuit or of just the oxygenator is possible. There is almost no evidence to suggest that one type of heparin coating or coating the entire bypass circuit provides superior benefit in blood transfusion or in postoperative bleeding despite numerous studies on the subject [388–410]. The exact mechanism of benefit from heparin-coated bypass circuits is uncertain. There are contradictory reports suggesting that heparin coating of the oxygenator or of the entire bypass circuit limits platelet activation [403, 411–413], reduces complement activation [414–418], alters cellular adhesion to the bypass tubing [419], or diminishes the inflammatory pulmonary injury seen after CPB [420, 421]. No clear-cut preference to one particular type of heparin coating arises from these touted advantages.

Several studies have evaluated bleeding and blood transfusion in patients having CPB with heparin-coated circuits or oxygenators. Most reports suggest that synthetic coating of the bypass circuit limits bleeding and blood transfusion after cardiac operations [392, 395–402], but other reports suggest otherwise [403–410]. The studies are too heterogeneous to be subjected to meta-analyses, as many studies use different heparin coating, different heparin doses, or different perfusion techniques. There is no consistent evidence that heparin coating either of the entire bypass circuit or of the oxygenator is preferred. Use of heparin bonded circuits appears to be safe and may provide some savings in blood use, but more information is required to justify a high-level recommendation for their use.

One proposed advantage of coating of the bypass circuit with heparin is the ability to reduce the heparin dose given to patients during CPB and consequently reduce the protamine dose used to neutralize heparin. Heparin effect is monitored during CPB with the ACT. An ACT value of greater than 400 s is used as the traditional standard for safe CPB, based largely on a primate study done in 1978 using bubble oxygenators [422]. There is no single "best" ACT level or standard that can be agreed upon from available literature. For extracorporeal circulation, heparin is necessary but may have harmful side effects, especially to platelet function [423]. Because of concerns about harmful effects of heparin, several investigators proposed reduced heparin to maintain an ACT level of approximately 300 s as a safe alternative that limits heparin exposure and protamine reversal [374, 398, 424, 425]. Numerous studies evaluated the impact of reduced heparin dose and heparin-coated circuits on postoperative bleeding and blood transfusion without a clear consensus arising [391, 392, 395–402, 426–436]. Again, the studies are too heterogeneous to lend themselves to meta-analysis, but no clear-cut advantage in blood conservation accrues to low-dose heparin for patients perfused with heparin-coated circuits. One study suggests that lower doses of heparin are associated with increased bleeding after operation [377]. Many investigators in the field of blood conservation point out that

a multimodality approach that includes preoperative risk reduction, perioperative blood salvage and blood sparing, and careful attention to postoperative transfusion algorithms is the most successful strategy for blood conservation [49, 264, 437, 438]. With so many interventions playing a small part in a multimodality program, it is unlikely that a single intervention will stand out unless there is unquestioned efficacy or a very large sample size is considered in a randomized clinical trial. To date, a large enough clinical trial has not been conducted to answer the question of whether heparin-coating with or without low-dose heparin limits blood transfusion, and high-level evidence to support this intervention does not exist.

Three cautionary notes should be mentioned in conjunction with low-dose heparinization during CPB. Reports suggest that increased thrombin may be generated when lower doses of heparin are used during CPB [431, 436]. Increased thrombin generation is almost certainly associated with increased platelet activation during CPB and may result in increased blood loss [439]. Differences in perioperative bleeding in patients with small increases in thrombin generation may be hard to detect and may only become apparent at longer or more difficult bypass runs. Second, because of important blood conservation properties of antifibrinolytic agents like aprotinin, patients in whom low-dose heparin is used may be at increased risk with certain of the antifibrinolytic agents, especially if circulatory arrest is a prominent part of the operation [440, 441]. There is limited support for using the combination of low doses of heparin in conjunction with antifibrinolytic agents during CPB (with or without heparin-coated bypass circuits). Third, preliminary evidence suggests that heparin coating induces gene expression changes in the perfused cellular elements after CPB to a greater extent than protein (albumin) coated circuits [442]. Whether changes in gene expression play a role in blood conservation is uncertain, and only time will tell what impact this has on bleeding. Because of these concerns and the lack of compelling safety data, low doses of heparin during the conduct of CPB should be used with caution.

VII)   RED CELL AND PLATELET SAVING

Class I

1. **Routine use of red cell saving is helpful for blood conservation in cardiac operations using CPB, except in patients with infection or malignancy. (Level of evidence A)**

Class III

1. **Routine use of intraoperative platelet or plasmapheresis is not recommended for blood conservation during cardiac operations using CPB. (Level of evidence A)**

Intraoperative salvage of red blood cells, using a cell saving apparatus, is an important part of blood con-

servation in cardiac operations using CPB. Beginning in the mid 1970s, commercially available cell-saving devices became available for routine use in cardiac and other high-risk operations. Several reports document the safety of red blood cell saving. Specifically, no adverse CNS events [443], no increased infectious complications [444], no increased hemolysis or fat emboli [445], reduced circulating markers of systemic inflammation with removal of most [446] but not all [447] cytokines from suctioned blood, and overall reduced complication rates [448] are associated with intraoperative use of red cell savers. At least 10 published reports, including some randomized controlled trials, support the routine use of red blood cell saving to reduce bleeding and blood transfusion, although the reduction in transfusions may be modest [449–458]. However, extensive use of cell salvage systems to process contents of the extracorporeal circuit after discontinuation of CPB or with processing of extensive quantities of cardiotomy-derived blood may lead to a critical loss of coagulation factors and platelets, resulting in a bleeding diathesis. This is supported by a multivariate analysis that demonstrated that processed cell salvage volumes were related to bleeding/transfusion [377]. With usual red blood cell saving protocols, about half of the blood suctioned from the patient is ultimately reconstituted. With careful attention to intraoperative hemostasis in patients at low risk for operative bleeding, it may be that use of a cell-saving device is not a cost-effective measure, although most assessments of cost favor routine use of cell-saving devices [459–461]. Presence of malignancy, infection, or blood exposed to topical clotting agents (eg, thrombostat, fibrin glue, Tisseal, Gelfoam, or any other thrombin-containing compound) are contraindications to use of the cell-saving device.

Platelet-rich plasmapheresis is a continuous centrifugation technique, using technology similar to red cell savers that allows selective removal of platelet rich plasma from the circulating whole blood immediately before the start of CPB. As platelet dysfunction is a prominent part of CPB-induced coagulopathic bleeding, it seemed reasonable to remove platelets from the stress of CPB and return these "spared platelets" to the patient at the end of operation. This technique has the theoretical advantage that improvement in platelet number and function might limit postoperative bleeding without a decrease in oxygen carrying capacity. By varying the centrifugation technique, it is possible to obtain fractions that are either rich or poor in platelets [462, 463].

At least 18 studies [463–480] and one meta-analysis [481] evaluated the efficacy of platelet-rich plasmapheresis in limiting bleeding and blood transfusion after cardiac operations. The highest quality studies that involved blinding and randomization showed no benefit from this intervention [472–474, 479], whereas other published reports showed some benefit of platelet-rich plasmapheresis. For several reasons, platelet-rich plasmapheresis is not used clinically to any sig-

nificant extent. First, prophylactic transfusion of fresh platelets does not alter bleeding and blood transfusion after operations [482, 483], so there is no reason to suppose that platelets preserved by platelet-rich plasmapheresis will have a beneficial effect on postoperative hemostasis. Further, there is evidence that intraoperative autologous donation of fresh whole blood provides the same or better platelet preservation and blood-sparing effect as perioperative platelet-rich plasmapheresis [484, 485]. Likewise, platelet-rich plasmapheresis precludes the use of whole blood intraoperative autologous donation. The process of platelet-rich plasmapheresis is labor intensive and any technical mistakes in harvesting results in lost blood volume and platelet number, a potentially problematic occurrence that alters blood conservation adversely. If for some technical reason platelet-rich plasmapheresis is attempted but the blood removed from the patient is unable to be reinfused, this constitutes an iatrogenic mishap that is directly related to the intervention and is harmful, potentially resulting in additional transfusion. This event may occur as often as 1 in 30 times [471]. Given that platelet-rich plasmapheresis is labor intensive, costly, of marginal benefit, and possibly more risky than whole blood intraoperative autologous donation, this technique can not be recommended for routine use in blood conservation during cardiac procedures.

VIII) LEUKOCYTE FILTRATION

Class III

1. **Leukocyte filters on the CPB circuit for leukocyte depletion should not be used for perioperative blood conservation and may actually activate leukocytes during CPB. (Level of evidence B)**

Many of the harmful effects of CPB can be traced to leukocyte activation during extracorporeal perfusion. Temporary removal of white blood cells around the time of CPB may limit some of this damage. Various leukocyte filters are available for use in conjunction with the perfusion apparatus. These filters are capable of depleting the systemic circulation of leukocytes and possibly improving organ function after operation. Improved neutrophil adhesion [486], better endothelial function [487] and lung function [488], limitation of reperfusion injury [489], reduced rate of atrial fibrillation [490], and improvement in brain function after circulatory arrest [491] are putative benefits attributed to use of leukocyte depletion during various stages of CPB. None of these observed beneficial effects translates into consistent, significant clinical benefit [67, 492–495]. There is evidence that leukocyte depletion during CPB may, in fact, activate white cells [496, 497]. Because of the lack of clinical benefit and the concerns about worsening leukocyte function with leukocyte depletion, this methodology cannot be recommended for blood conservation during CPB.

c) Perfusion Techniques and OPCAB

I) MINIMIZED EXTRACORPOREAL BYPASS CIRCUITS

Class IIb

1. **It is not unreasonable to use low prime and minimized extracorporeal bypass circuits to reduce the fall in hematocrit during CPB as part of a multimodality blood conservation program. (Level of evidence B)**

Minimized, and sometimes integrated (combined centrifugal pump and oxygenator), low prime (450 to 800 mL), reduced surface area extracorporeal circuits are used clinically. Authors report less hemodilution and reduced inflammatory response with these minimized circuits [498–503]. Abdel-Rahman and coworkers [503] report reduced activation of coagulation and fibrinolysis with minimized bypass circuits and suggest a benefit in reduced transfusion associated with these circuits. One retrospective comparison of 970 patients undergoing elective CABG [499] and two prospective randomized studies by the same group [500, 501] of 400 patients undergoing elective CABG and 100 patients undergoing aortic valve replacement reported at least a 50% reduction in red blood cell transfusion rates with use of minimized circuits compared with conventional circuits. On the other hand, two smaller RCTs of 30 and 204 patients undergoing CABG found no decrease in transfusion requirements with use of two commercially available minimized circuits [502, 504]. Possible transfusion benefits from minimized circuits must be balanced against possible risks including air embolism, and lack of cardiotomy suction associated with this technology [504].

II) ACUTE NORMOVOLEMIC HEMODILUTION (ALSO CALLED INTRAOPERATIVE AUTOLOGOUS DONATION)

Class IIb

1. **Acute normovolemic hemodilution (ANH) is not unreasonable for blood conservation but its usefulness is not well established. It could be utilized as part of a multipronged approach to blood conservation. (Level of evidence B)**

This technique involves removal of one to two units of blood immediately before surgery and is used in a variety of fields of surgery including orthopedic surgery and general surgery. In the context of cardiac surgery, typically one to two units of autologous blood are removed immediately before the institution of cardiopulmonary bypass. Unstable patients are not appropriate candidates for this technique, especially in the presence of evolving acute myocardial infarction, unstable angina, or cardiogenic shock. Other typical exclusion criteria include patients with significant preoperative anemia, sepsis or known bacteremia. Relative contraindications may include low ejection fraction (< 30%) [505, 506]. To maintain circulating blood volume, the volume of blood removed is usually replaced 1:1 with crystalloid or colloid. During subsequent cardiopulmonary bypass, hematocrit on bypass determines transfusion. Transfusion of the

sequestered autologous units is the first source of replacement, followed by transfusion of allogeneic blood if the desired minimum hematocrit on bypass cannot be maintained with use of autologous blood. The use of ANH as a blood conservation method in surgery is based on the principle that lowering the red blood cell concentration (hematocrit) during surgery will decrease the reduction in red cell mass lost for any given volume of blood lost. The expected reduction in the need for allogeneic blood product administration is desirable to minimize the risk of transmission of hepatitis, HIV, other viral and bacterial pathogens, and immunomodulation induced by allogeneic red cell transfusion. In cardiac surgery, ANH has the additional theoretical advantage that the blood removed from the bypass circuit before the institution of CPB is "protected" from the potential deleterious effects of platelet activation and consumption, hemolysis, complement activation, and the production of a variety of inflammatory cytokines including interleukin 6, interleukin 8, and tumor necrosis factor alpha associated with extracorporeal circulation [507].

Several prospective randomized trials show a significant decrease in the transfusion rate of allogeneic blood products using this technique [508, 509] while others fail to document any benefit [443, 505, 510]. In a recent study by Hohn and associates [505], 80 adult patients who underwent cardiac surgical procedures were randomized to receive ANH or usual blood conservation care. All patients in both groups underwent standard blood conservation procedures including use of a cell-saving device, reinfusion of mediastinal shed blood, administration of intravenous aprotinin, and reinfusion of blood contained in the extracorporeal circuit after surgery. Acute normovolemic hemodilution harvested an average of 1,099 cc blood to achieve a calculated hematocrit of 28% after the induction of anesthesia. There was no statistical difference in the number of allogeneic units of blood transfused or in the percentage of patients (29%, control; and 33%, ANH) requiring blood transfusion. Casati and associates [443], in a study of "low volume" ANH randomly assigned 204 patients to ANH (5 to 8 mL/kg removed before heparinization therapy) or control (no ANH). These authors found no difference in the frequency or number of transfusions between the two groups [443]. Although both of these studies yielded negative results, the study by Hohn was criticized for excessive hemodilution with colloid and crystalloid after ANH such that more than 50% of the ANH patients received all (33%) or a portion (22%) of the autologous blood back during CPB.

The results of the study by Casati and associates [443] may be of limited relevance as "low volume" ANH is not the optimal strategy to use, based on mathematical models of ANH efficacy [511, 512], and since these authors routinely use aprotinin, further limiting the potential benefit of ANH in reducing transfusion requirements. Additionally, a recent randomized trial of ANH in patients undergoing liver resections showed a statistically significant reduction in the frequency of transfusion (10% versus 36%, $p < 0.05$) in the patients who received

ANH [471], but a meta-analysis yielded inconclusive results [513]. Retrospective studies of the efficacy of ANH in adult cardiac surgery are equally divided among those demonstrating benefit [514–516], and those failing to document a reduction in bleeding or in transfusion requirements [517, 518]. A cautionary note is worth mentioning. If for some technical reason ANH is attempted but the blood removed from the patient is unable to be reinfused, this constitutes an iatrogenic mishap that is directly related to the intervention and is potentially harmful, resulting in additional transfusion. This event may occur as often as 1 in 30 times with ANH [471]. Furthermore, patients who most need blood conservation are least likely to be candidates for ANH, as preoperative anemia and low blood volume are contraindications for this technique. For noncardiac surgery, with very aggressive red cell harvest, ANH may be efficacious and cost effective [519], but for cardiac procedures, the benefit of ANH is less well established, especially with aggressive red cell harvest. Care is necessary using ANH as it can be detrimental and is not likely to contribute significantly as the sole blood conservation intervention.

Combinations of ANH with other blood conservations may be beneficial. For example, use of synthetic fluorocarbons or hemoglobin based oxygen carrier products in conjunction with ANH shows clinical promise in most published trials [520–524]. Additionally, several studies suggest that a combination of blood conservation interventions is likely to provide the best reduction in blood transfusion [469, 525–530]. It is entirely possible that the effect of the combinations of blood conservation interventions that include ANH may be more beneficial than the sum of the individual components. Any strategy for limiting excessive blood transfusion after cardiac procedures should identify the institution-specific blood conservation interventions that are efficacious and employ these interventions in combination, especially for the high-risk subset of patients. Institution-specific risk/benefit profiles are essential to optimize blood conservation.

III)   PUMP SALVAGE AND INTRAOPERATIVE AUTOTRANSFUSION

Class IIb

1.   **During CPB, it is not unreasonable to use intraoperative autotransfusion, either with blood directly from cardiotomy suction or recycled using a cell-saving device, to augment blood conservation. (Level of evidence C)**
2.   **Shortly after the completion of cardiopulmonary bypass, salvage of pump blood, either administered without washing or after washing with a cell-saving device, is not unreasonable as a means of blood conservation. (Level of evidence C)**

The autotransfusion of mediastinal blood from the operative field during CPB is routinely performed during adult cardiac surgical procedures. In cases of rapid hemorrhage, reinfusion of blood using the cardiotomy suction device can be lifesaving. However,

"uncontrolled" cardiotomy suction during prolonged cardiopulmonary bypass (longer than 3 hours) is associated with an increase in postoperative bleeding compared with "controlled" cardiotomy suction designed to minimize the associated aspiration of air [531]. Intraoperative autotransfusion that employs a cell-saving device is capable of collecting blood both when the patient is heparinized and during periods where no heparin effect is present (eg, during internal thoracic artery harvest) and the benefits of cell-saving device use are discussed above. Suction of mediastinal blood during CPB risks entrapment of particulate matter, especially fat, and some evidence exists that cardiotomy suction for autotransfusion is a source of fat emboli to the brain during CPB [532]. Reents and coworkers [507] suggest that contamination with bacteria is more common with cell-saved autotransfusion than with direct cardiotomy suction. Risks from autotransfusion during CPB are equal among the various methods used to recycle mediastinal blood.

Surprisingly there is no evidence-based preference for any form of intraoperative autotransfusion during CPB. There does not seem to be a difference in blood transfusion after autotransfusion using a cell-saving device only during CPB versus autotransfusion with direct cardiotomy suction [445, 533–537]. Two studies compared autotransfusion using a cell-saving device to discard of cardiotomy suctioned blood during CPB [538, 539], with only the study of Nataf and coworkers [538] suggesting a benefit in blood conservation from cell-saving–aided autotransfusion during CPB. Based on available evidence, only a weak recommendation for autotransfusion during CPB, either with cell saving or with cardiotomy suction, can be made.

Salvage of pump blood at the completion of cardiopulmonary bypass is routinely performed in most centers. There are limited data available on the impact of this practice on the requirement for allogeneic blood transfusion. Six studies address the benefit of salvage of blood from the heart-lung machine at the end of CPB (pump salvage) with mixed results [536, 540–544]. The studies are too heterogeneous and underpowered to draw firm conclusions, but consensus favors the routine use of some form of pump blood salvage at the end of CPB. Discarding or purification (ie, use of cell-saving devices) of cardiotomy-derived mediastinal blood is not clearly beneficial for blood conservation, but loss of coagulation factors and platelets may be potentially detrimental with resultant excessive bleeding. Whether pump salvage using a cell-saving device or using direct reinfusion, most surgeons agree that discarding the residual pump blood wastes a potentially valuable resource. No study suggests that pump salvage results in serious injury, so the risk/benefit ratio favors some form of reinfusion of residual blood from the heart-lung machine, although with virtually no evidence.

IV) POSTOPERATIVE SHED BLOOD REINFUSION

Class IIb

1. **Postoperative mediastinal shed blood reinfusion using washed mediastinal blood (cell saving) is not**

unreasonable 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 is not unreasonable to limit blood transfusion as part of a multimodality blood conservation program. (Level of evidence B)

Class III

1. **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)**

Studies using postoperative reinfusion of shed mediastinal blood to limit blood transfusion first appeared in the early 1970s. Since then, 17 reports provided conflicting results about the benefit of this intervention [543, 545–561]. Nine of these 17 studies suggest that postoperative shed blood reinfusion limits blood transfusion [543, 546, 547, 549, 551, 556, 557, 559, 561], and the rest do not. These studies are heterogeneous as some compared washed (cell saved) versus nonwashed (cardiotomy reservoir) postoperative shed mediastinal blood reinfusion while others compared either of these techniques to simply discarding shed mediastinal blood. In addition, mediastinal blood contains fibrinolytics, inflammatory cytokines, complement, endotoxin, tissue factor, and free hemoglobin [443, 507, 531, 547, 552, 554, 561–565]. Infusion of shed mediastinal blood results in activation of the extrinsic coagulation pathway [443, 554, 565], although washing of mediastinal blood may reduce these abnormalities [507, 563]. Furthermore, mediastinal blood contains lipid particles and thromboemboli that are incompletely removed by existing blood filters, and these impurities are postulated to contribute to neurologic dysfunction after cardiac surgery [291, 566, 567]. Use of a cell-saving device to wash shed mediastinal blood results in a significant decrease in lipid emboli and in inflammatory cytokines in the reinfused blood compared with blood obtained directly using a cardiotomy reservoir [507, 563, 568]. Importantly, two studies suggest that postoperative unwashed shed blood reinfusion is associated with increased sternal or systemic infections [545, 548]. Because of the risks associated with this technique and the lack of clear cut benefit, direct reinfusion of shed blood can not be recommended for routine blood conservation; whereas, postoperative reinfusion of washed shed mediastinal blood may be helpful as part of a multimodality blood conservation program.

V) PREOPERATIVE AUTOLOGOUS BLOOD DONATION

Class IIa

1. **Predonation of as much as two units of autologous blood is reasonable for blood conservation in carefully selected (mostly elective) patients before routine cardiac operation particularly when coupled with appro-**

priately dosed erythropoietin (EPO) therapy and/or iron therapy. (Level of evidence A)

Autologous blood donation a few days to a few weeks preoperatively is commonly practiced for a variety of noncardiac surgical procedures to reduce the requirement for allogeneic blood transfusion. This practice is not routinely employed for patients undergoing cardiac surgery, owing in part to concerns about a possible increase in the incidence of myocardial infarction or hemodynamic instability during the period after predonation but before surgery. Nonetheless, there is an increasing body of literature [445, 569–577] documenting the safety of this practice and a significant reduction in the transfusion of allogeneic blood products associated with this practice in selected patients undergoing cardiac surgery, particularly when performed concomitantly with erythropoietin and/or administration to allow for a compensatory increase in red cell production [572–574, 578]. However, the cost effectiveness and benefit/risk ratio of this technique has been questioned [579, 580]. Further, the use of EPO to augment red cell production during preoperative autologous donation in patients having cardiac procedures is not recommended by the drug manufacturers because of limited safety data. Hence, the use of EPO in this circumstance has an unproven safety profile and is an "off-label" application of this drug.

VI) RETROGRADE AUTOLOGOUS PRIMING OF THE CARDIOPULMONARY BYPASS CIRCUIT

Class IIb

1. **Retrograde autologous priming of the CPB circuit is not unreasonable for blood conservation. (Level of evidence B)**

This method replaces the crystalloid prime volume of the cardiopulmonary bypass circuit with the patient's own blood immediately before beginning cardiopulmonary bypass [458, 581–583]. Typically, the arterial limb of the circuit is cleared retrograde through back bleeding from the aortic cannula, and the venous limb is cleared antegrade using the blood pump. The displaced crystalloid is collected and excluded from the circuit. A cautionary note needs to be added. The connection of a patient to a vacuum assisted venous drainage system for retrograde autologous priming (ie, with a closed hard shell reservoir) is a potentially dangerous situation. On at least one occasion, this resulted in massive systemic air embolism through a patent foramen ovale, and vacuum-assisted venous drainage should not be used for retrograde autologous priming. This technique maintains colloid osmotic pressure and reduces extravascular lung water compared with standard priming techniques [458]. In two of three randomized trials, retrograde autologous priming caused a significant reduction in the frequency of allogeneic blood transfusion compared with usual practice [458, 582, 583]. Two other studies showed a trend toward lower usage of allogeneic blood transfusions but did not reach statistical significance [458, 581].

VII) HEMOFILTRATION

Class IIb

1. **Use of modified ultrafiltration is not unreasonable for blood conservation during CPB in pediatric patients or in patients where the priming volume is a very significant fraction of the total blood volume. (Level of evidence B)**

Class III

1. **Routine use of ultrafiltration during or immediately after CPB is not helpful for blood conservation in adult cardiac operations. (Level of evidence B)**

Both conventional ultrafiltration (CUF) and modified ultrafiltration (MUF) are employed in cardiac surgery. The rationale behind the use of CUF is that this technique represents a method to remove the excess fluid associated with the priming volume needed for cardiopulmonary bypass. However, because additional crystalloid or blood are often added to the circuit to maintain adequate circulating volume during CPB, the results of this technique are inconsistent with regard to reducing total body water but are generally associated with a reduction in the systemic concentration of inflammatory mediators [584]. Modified ultrafiltration has been studied most extensively in pediatric cardiac surgical patients and results in statistically significant reductions in TBW, removal of inflammatory mediators, and improvement in hemodynamic indices [584–587]. The improved efficacy of MUF probably relates to the fact that it is performed for a period of time after CPB is completed. There are several prospective randomized studies of CUF and MUF in adult patients [588–593], including two studies that compared CUF alone [589, 593], two studies that compared MUF alone [590, 591], and two studies that compared CUF combined with MUF to conventional CPB without ultrafiltration [588, 592]. In a study of 60 patients randomly assigned to CUF versus standard CPB, there was no difference in allogeneic blood product usage [593]. Similarly, in a randomized study of 97 patients comparing MUF alone to conventional CPB, there was no difference in blood loss between the two groups, although there was a significant reduction in adhesion molecules and cytokines in the MUF group [591]. One study demonstrated a significant reduction in postoperative blood loss in the group that was randomly assigned to CUF combined with MUF, and although there was no difference in the amount of allogeneic blood transfused, there was a significant reduction in the transfusion of fresh frozen plasma compared with control high-risk adult patients [588]. A retrospective study of 61 patients who received CUF alone compared with 57 patients who received conventional CPB for high-risk adult cardiac procedures showed a trend toward decreased bleeding in the CUF group [594]. Because of the lack of consistent benefit of CUF in limiting blood transfusion in adults during CPB, this

technique is not likely to be helpful for blood conservation.

VIII) OFF-PUMP PROCEDURES FOR BLOOD CONSERVATION

Class IIa

1. **Off-pump coronary artery bypass (OPCAB) is a reasonable means of blood conservation, provided that emergent conversion to on-pump bypass is unlikely either based on surgeon experience or patient characteristics. (Level of evidence A)**

Several randomized trials, and two meta-analyses compared the results of OPCAB to on-pump coronary revascularization [56, 595–600]. In general, these studies show a reduction in the use of allogeneic blood transfusions with OPCAB [56, 595–598, 600]. One study showed no difference in the total postoperative blood loss between the two techniques while documenting a significant decrease in the use of packed red blood cell transfusions [595]. Another study showed no significant difference in the number of allogeneic units transfused or in the postoperative blood loss between the two groups [599]. Looking at the data more carefully shows that the number of patients who crossed over from OPCAB to on-pump was not uniform among these reports. In the studies by Puskas and associates [598], Khan and associates [595], van Dijk and associates [596], and Angelini and associates [597], crossovers to on-pump CABG were rare, occurring in 1%, 4%, 7%, and 1% of patients, respectively. In contrast, in the one randomized trial that showed no difference in transfusion requirements or blood loss between on-pump and OPCAB groups, crossovers from OPCAB to on-pump were more common, occurring in 22.5% of patients [599]. Also, many of the retrospective studies that have demonstrated decreased blood loss and decreased transfusion requirements with OPCAB have not included cross-over patients in the off-pump group as an intention-to-treat analysis would require [601]. Every unfavorable outcome, including bleeding requiring reoperation, was more common in the emergency OPCAB to on-pump conversion subgroup. This is distinctly different than patients in whom OPCAB without emergency conversion was performed [601].

d) Topical Agents/Tissue Glues

Class IIb

1. **Topical sealants used to assist in the repair of complex, high-risk cardiac and aortic procedures are not unreasonable to limit bleeding in certain key situations (eg, left ventricular free wall rupture and aortic dissection) but are associated with complications that may limit their usefulness in less high risk situations. (Level of evidence C)**

Class III

1. **Topical hemostatic agents that employ bovine thrombin are not helpful for blood conservation during CPB and may be potentially harmful. (Level of evidence B)**

Numerous topical hemostatic agents are available for use during cardiac operations. The wide variation of these topical agents, including some "home remedies," makes an evidence-based comparison impossible. There is almost no evidence to support the routine use of these agents for blood conservation. What little evidence exists is in the form of anecdotal or noncontrolled reports with little indication of benefit, other than subjective appraisal [602, 603]. One randomized multicenter trial studied the use of fibrin sealant for topical hemostasis. This trial found no benefit in blood conservation for fibrin sealant [604].

Bovine thrombin is a commonly used topical hemostatic agent in vascular and cardiac operations. This agent causes a profound immunologic response [605–608], especially in children, and is associated with worse clinical outcome without much benefit in blood conservation in most cases [608, 609]. Antibodies generated to bovine thrombin can be a problem if reexposure to thrombin occurs soon after the initial exposure [608, 609]. Use of topical bovine thrombin cannot be recommended because of the potentially harmful immunologic reactions that may occur with this drug. Likewise, some of the topical hemostatic agents contain aprotinin, especially those manufactured in Europe. The use of aprotinin in topical hemostatic agents risks the potential of sensitization of patients to this agent and subsequent reexposure to aprotinin, especially within 6 months of initial dosing, carries a 5% incidence of some hypersensitivity reaction, most commonly anaphylaxis [249, 610]. Because of the unrecognized prior exposure to aprotinin, development of a careful drug history and other precautioinary steps are essential before using aprotinin for blood conservation [611].

Fibrin glue preparations, with or without the addition of bovine thrombin, are used extensively in complex operations on the aorta, especially in Europe [612–615]. A few cautionary notes surfaced after this extensive use. One report documents interference with prosthetic aortic valve function by fibrin glue used for aortic repair [616]. Fibrin glue in the pericardium does not reduce pericardial adhesions but has been sprayed in the pericardium for this reason [617]. Two reports document the occurrence of aortic redissection upon mid-term follow-up after resorcinol tissue sealants were used in the repair of a type A aortic dissection [618, 619].

Left ventricular free wall rupture after myocardial infarction or during mitral valve operations is a devastating problem with a high associated mortality [614, 620]. Fibrin sealants in conjunction with pericardial or synthetic covering are used to seal the rupture site [614, 621, 622]. Not all fibrin glues provide mechanical strength in addition to hemostatic support and, in fact, most sealants available in the United States do not provide enough mechanical strength for this purpose [623]. While the extensive use of these agents in these high-risk opera-

Table 6. Summary of Recommendations for Perioperative Prophylactic Measures for Blood Conservation

Recommendation	Level of Evidence	Class
Preoperative screening of the intrinsic coagulation system is not recommended unless there is a clinical history of bleeding diathesis.	B	III
Screening preoperative bleeding time is not unreasonable for high-risk patients, especially those who receive preoperative antiplatelet drugs.	B	IIb
Preoperative hematocrit and platelet count are indicated for risk prediction, and abnormalities in these variables are amenable to intervention.	A	I
Devices aimed at obtaining direct hemostasis at catheterization access sites are not unreasonable for blood conservation if operation is planned within 24 hours.	C	IIb
Alternatives to laboratory blood sampling (eg, oximetry instead of arterial blood gasses) are reasonable means of blood conservation before operation.	C	IIa
A comprehensive, integrated, multimodality blood conservation program in the intensive care unit is a reasonable means to limit blood transfusion.	B	IIa

tions is unproven, the potential benefits outweigh the risks, and consensus favors their use only for these potentially lethal conditions.

6) Prophylaxis—Interventions Outside the Operating Room

Many interventions that influence blood conservation occur before operation. These interventions can occur in the catheterization laboratory, in the ICU, or even in the outpatient setting. The team dedicated to blood conservation should hold discussions with cardiology to coordinate an institution-wide approach for cardiovascular patients. Table 6 and the following discussion summarize some of the important evidence-based perioperative findings that impact blood conservation.

a) Catheterization Laboratory Interventions

Catheterization access site complications are common, ranging from minor hematomas to major vascular compromise [118, 624–629]. Access site complications occur 1% to 9% of the time depending on the complexity of the percutaneous procedure [628]. Five percent of patients will require a transfusion after catheterization. One multicenter randomized controlled trial [630] and one cohort study [627] looked at the method used to manage access site control after catheterization, with no significant difference in hematomas and bleeding complications identified from any technique. A prospective multicenter clinical nursing trial of 4,010 patients revealed that nursing interventions employed did not significantly decrease

bleeding at the groin access site [631]. Access site complications are more common if potent antiplatelet agents are used during the procedure [118]. Given the low but fairly constant rate of access site bleeding complications from catheterization, consensus suggests that closure devices or collagen plug devices that directly control bleeding at the access site are preferred in patients who require operation within 24 hours of catheterization (Table 6). This is a preoperative blood conservation adjunct that may prevent unrecognized blood loss at the access site during CPB with high-dose systemic heparinization. In the case of CPB, high-dose heparin is a hematologic stress equivalent to that of high-intensity antiplatelet therapy, and consensus suggests that direct closure devices at the catheterization site are not unreasonable to limit bleeding and blood transfusion related to recent catheterization (within 24 hours) at the time of cardiac procedures using CPB [118, 628]. Other interventions aimed at limiting blood loss around the time of cardiac catheterization will optimize preoperative red cell mass and ultimately decrease blood transfusion after operation.

b) Preoperative Laboratory Testing

In the preoperative evaluation, thoughtful application of laboratory tests and associated blood draws are likely to conserve blood. Scher [632] looked at 30 patients who underwent reoperation for postoperative bleeding and showed that bleeding occurred despite normal preoperative prothrombin and partial thromboplastin times and adequate platelet counts. A retrospective chart review of 82 patients requiring exploration for bleeding showed limited correlation of preoperative coagulation testing with postoperative coagulopathy [633]. Routine screening of the intrinsic coagulation system is likely to be unrewarding unless there is a clinical history of bleeding diathesis found on preoperative screening.

The utility of preoperative bleeding times as a screening tool for blood conservation is controversial. One study showed that an *in vitro* bleeding time device may be a convenient and useful tool to examine primary hemostasis or platelet function in some patients [634]. A prospective study in 219 liver biopsies concluded that the bleeding time may give additional information on the risk of periprocedural bleeding in patients at high-risk for surgical bleeding. An observational study in patients having a broad spectrum of cardiac procedures suggested that bleeding time was an important multivariate predictor of excessive postoperative bleeding [20]. In contrast, a retrospective review of 1,941 bleeding times showed that prolongation of the bleeding time may not always be associated with excessive surgical blood loss [635]. Four prospective investigations of bleeding times and bleeding, with study sizes of 118,636, 43,637, 167,638, and 112,639, all showed that prolonged bleeding times are not associated with clinically significant perioperative bleeding and are not a reliable routine screening test. Furthermore, a position paper by the College of American Pathologists and American Society of Clinical Pathologists states that in the absence of a history of excessive

bleeding or other high-risk features like preoperative antiplatelet therapy, the bleeding time fails as a routine screening test [640]. Use of the bleeding time test in preoperative patients can only be recommended for patients at high risk for postoperative bleeding [17]. A potential advantage of the bleeding time test is that an abnormally prolonged bleeding time may be one of the reversible causes of excessive postoperative hemorrhage. If a prolonged test is due to drug effect, it is possible to correct the hemostatic defect by simply delaying operative intervention until the drug effect wears off and the bleeding time returns to the normal range.

Preoperative hematocrit can be used as part of the prediction of risk of blood transfusion, as demonstrated in a prospective study of 1,007 patients [26]. Furthermore, preoperative screening of 1,221 patients suggested that one of the few preoperative risks that can be targeted to reduce postoperative blood transfusion was anemia and low red blood cell volume [641]. Screening for preoperative anemia is likely to suggest cost- and risk-reduction strategies.

c) Intensive Care Unit Processes and Practices

Many ICU practices contribute to preoperative blood loss and ultimately to postoperative blood transfusion. Corwin and associates [642] showed that phlebotomy contributes significantly to a large number of transfusions in 142 ICU patients with an ICU length of stay of longer than 1 week. The equivalent of 30% of the total blood transfused was phlebotomized from patients during their ICU stay. Blood conservation methods including use of small-volume tubes, elimination of arterial line blood discard, and elimination of standing orders for laboratory tests decreased phlebotomy blood loss by 33% to 47% [642]. Small volume (pediatric) phlebotomy tubes and reduced syringe volumes saved lost blood volume by as much as 45% [643, 644]. In addition to smaller phlebotomy volumes, the pattern of laboratory test use can be reduced to minimize the sampling. Drawing as few blood specimens as possible was part of a blood conservation program for a study of 50 Jehovah's Witnesses [645] (referenced by Groom [437]). A prospective study of 190 patients tested a multimodality blood conservation program against "standard" measures in a control group. The multimodality conservation program included use of pediatric blood tubes, returning all arterial line flushes, and minimizing laboratory sampling. The blood conservation program significantly decreased bleeding and need for allogeneic transfusion, in a safe and cost-effective manner [530].

Other blood conservation modalities in critical care monitoring include use of oximetry instead of intra-arterial blood gas monitoring systems [646]. Three prospective studies looked at the efficacy of a new blood conserving intra-arterial blood gas system, which gave reliable, accurate, and blood-conserving results. Zimmerman and Dellinger [647] studied 104 arterial blood gas samples in 5 patients, whereas two institutions conducted larger prospective clinical trials [648, 649]. These studies suggest that an intra-arterial

system that monitors oxygen saturation is beneficial in limiting blood loss from arterial blood gas determinations in the ICU.

A key aspect of ICU care and physician practice revolves around comprehensive, optimized, integrated, multimodality blood conservation programs. Several authors identified a multimodality ICU blood conservation program as a significant factor in reducing blood utilization [526, 530, 650, 651]. These studies emphasize the savings in blood transfusion that are caused by multiple blood conservation techniques (eg, pediatric blood tubes, oximetry instead of arterial blood gases, reduced frequency of blood testing, and so forth) implemented by a multidisciplinary team. These studies also demonstrate significant cost savings associated with these blood conservation interventions.

7) Transfusion and Blood Conservation Algorithms—the Multimodality Approach

Class I

1. A multimodality 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 (Table 7) will limit blood transfusion and provide optimal blood conservation for cardiac operations. (Level of evidence A)

Guidelines in general, and in particular for the management of bleeding during cardiac procedures, are available but are relatively unsuccessful in accomplishing change in practice, especially in limiting nonautologous blood transfusion [41, 160, 652, 653]. There is still marked variability in transfusion practices and blood conservation interventions. There are at lease two reasons for this failure of guidelines. First, accurate and timely information about the platelet and coagulation status of patients in the operating room or in the ICU is difficult to obtain. Second, patient, physician, and institutional process variability is difficult to control and manage. These shortcomings caused several investigators to evaluate transfusion algorithms in a prospective manner using institution-derived transfusion practices in conjunction with accurate point-of-care testing to guide responses to bleeding and to direct blood transfusion. In most [530, 654–658] but not all [659] studies, the combination of point-of-care testing and transfusion algorithms used to direct valuable blood resources was both cost effective and efficacious in limiting nonautologous blood product transfusions and providing adequate hemostasis. These studies include two randomized trials that support the use of point-of-care testing and transfusion algorithms to limit blood transfusion and enhance blood conservation [657, 658].

Multiple point-of-care tests were used in the analyses described above, and it is hard to recommend one over the other. Further, it is not clear whether the algorithms developed for guiding transfusion and the multidisciplinary approach are more important than the point-of-

Table 7. Recommendations for a Multimodality Blood Conservation Program

Recommendation	Class
Preoperative identification of high-risk patients (advanced age, preoperative anemia, small body size, non–coronary artery bypass graft (CABG) 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
High-dose aprotinin is indicated to reduce the number of patients requiring blood transfusion, to reduce total blood loss, and to limit reexploration in high-risk patients undergoing cardiac operations. Benefits of use should be balanced against the increased risk of renal dysfunction. (Level of evidence A)	I
Low-dose aprotinin is indicated to reduce the number of patients requiring blood transfusion and to reduce the total blood loss in patients having cardiac procedures. (Level of evidence A)	I
Lysine analogues like epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) are indicated to reduce the number of patients who require blood transfusion, and to reduce total blood loss after cardiac operations. These agents are slightly less potent blood-sparing drugs and the safety profile of these drugs is less well studied compared with aprotinin. (Level of evidence A)	I
Routine use of red-cell saving is helpful for blood conservation in cardiac operations using cardiopulmonary bypass (CPB), except in patients with infection or malignancy. (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
A multimodality 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 will limit blood transfusion and provide optimal blood conservation for cardiac operations. (Level of evidence A)	I
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
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
Routine prophylactic use of desmopressin acetate (DDAVP) is not recommended to reduce bleeding or blood transfusion after cardiac operations using CPB. (Level of evidence A)	III
Use of prophylactic positive end-expiratory pressure (PEEP) to reduce bleeding postoperatively is not effective. (Level of evidence B)	III
Routine use of intraoperative platelet or plasmapheresis is not recommended for blood conservation during cardiac operations using CPB. (Level of evidence A)	III
Leukocyte filters on the CPB circuit for leukocyte-depletion should not be used for perioperative blood conservation and may actually activate leukocytes during CPB. (Level of evidence B)	III
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
Routine use of ultrafiltration during or immediately after CPB is not helpful for blood conservation in adult cardiac operations. (Level of evidence B)	III
Topical hemostatic agents that employ bovine thrombin are not helpful for blood conservation during CPB and may be potentially harmful. (Level of evidence B)	III
Preoperative screening of the intrinsic coagulation system is not recommended unless there is a clinical history of bleeding diathesis. (Level of evidence B)	III
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
Patients who have thrombocytopenia (less than 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 for these high-risk patients. (Level of evidence B)	IIa
It is reasonable to discontinue thienopyridines 5 to 7 days before cardiac procedures to limit blood loss and transfusion. Failure to discontinue these drugs before operation risks increased bleeding and possibly worse outcome. Caution must be used with sudden withdrawal of antiplatelet therapy in the presence of drug-eluting stents. This can lead to stent thrombosis, and the surgical team should consider various alternatives to maintain stent patency. That could even include hospitalization to convert thienopyridine therapy to short-acting GP2b/3a inhibitors for a few days before operation. (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
With hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable as 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 non–red 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

Table 7. Recommendations for a Multimodality Blood Conservation Program (Continued)

Recommendation	Class
During cardiopulmonary bypass with moderate hypothermia, transfusion of red cells for a hemoglobin level ≤ 6 g/dL is reasonable except in patients at risk for decreased cerebral oxygen delivery (ie, history of cerebrovascular accident, diabetes mellitus, 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 variables (eg, hematocrit, SVO_2, electrocardiographic or echocardiographic evidence of myocardial ischemia, etc). (Level of evidence C)	IIa
In patients after cardiac operations with hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable and can be life-saving. Transfusion of red cells is reasonable in most postoperative patients with hemoglobin level of or less, 7 g/dL but no high-level evidence supports this recommendation. (Level of evidence C)	IIa
It is reasonable to transfuse non–red 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
Recombinant human erythropoietin (EPO) is reasonable to restore red blood cell volume in patients undergoing autologous preoperative blood donation before cardiac procedures. However, no large-scale safety studies for use of this agent in cardiac surgical patients have been performed. Available evidence suggests an acceptable safety profile. (Level of evidence A)	IIa
Recombinant human EPO is a reasonable alternative for anemic low-risk elective patients (hemoglobin ≤ 13 g/dL) before cardiac procedures provided that EPO is given in conjunction with iron therapy several days or more before operation. (Level of evidence B)	IIa
Predonation of as much as two units of autologous blood is reasonable for blood conservation in carefully selected (mostly elective) patients before routine cardiac operation, particularly when coupled with appropriately dosed EPO therapy and/or iron therapy. (Level of evidence A)	IIa
Off-pump coronary artery bypass (OPCAB) is a reasonable means of blood conservation, provided that emergent conversion to on-pump bypass is unlikely either based on surgeon experience or patient characteristics. (Level of evidence A)	IIa
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
A comprehensive, integrated, multimodality blood conservation program in the intensive care unit is a reasonable means to limit blood transfusion. (Level of evidence B)	IIa
Total quality management (TQM), 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
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 activation, streptokinase) are associated with increased bleeding after cardiac operations. It is not unreasonable to stop these medications before operation 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 a notable exception in that it is the only agent that may be discontinued shortly before operation or not at all. (Level of evidence C)	IIb
It is not unreasonable 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, it is not unreasonable to keep the hemoglobin level at ≥ 7 g/dL or higher. (Level of evidence C)	IIb
It is not unreasonable to use preoperative EPO, given at least a few days before operation, to increase red cell mass in elective patients who are at risk for postoperative anemia and depressed endogenous EPO production. (Level of evidence C)	IIb
Use of DDAVP is not unreasonable 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
Use of recombinant factor VIIa concentrate is not unreasonable for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB. (Level of evidence B)	IIb
A trial of therapeutic PEEP to reduce excessive postoperative bleeding is not unreasonable. (Level of evidence B)	IIb
It is not unreasonable to use open venous reservoir membrane oxygenator systems during CPB 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 is not unreasonable to prefer centrifugal pumps because of perfusion safety features. (Level of evidence B)	IIb

Table 7. Recommendations for a Multimodality Blood Conservation Program (Continued)

Recommendation	Class
For patients requiring longer CPB times (more than 2–3 hours), it is not unreasonable to consider maintenance of higher or patient-specific heparin concentrations during CPB to reduce hemostatic system activation, reduce consumption of platelets and coagulation proteins, and reduce blood transfusion. (Level of evidence B)	IIb
It is not unreasonable to 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 to reduce bleeding and blood transfusion requirements. (Level of evidence B)	IIb
Heparin-coated bypass circuits (either the oxygenator alone or the entire circuit) are not unreasonable for blood conservation in cardiac operations. (Level of evidence B)	IIb
Low doses of systemic heparinization (activated clotting time $\sim$ 300 s) are not unreasonable for blood conservation during CPB, but the possibility of underheparinization and other safety concerns have not been well studied. (Level of evidence B)	IIb
It is not unreasonable to use low prime and minimized extracorporeal bypass circuits to reduce the fall in hematocrit during CPB as part of a multimodality blood conservation program. (Level of evidence B)	IIb
Acute normovolemic hemodilution is not unreasonable for blood conservation, but its usefulness is not well established. It could be utilized as part of a multipronged approach to blood conservation. (Level of evidence B)	IIb
During CPB, it is not unreasonable to use intraoperative autotransfusion, either with blood directly from cardiotomy suction or recycled using a cell-saving device, to augment blood conservation. (Level of evidence C)	IIb
Shortly after the completion of cardiopulmonary bypass, salvage of pump blood, either administered without washing or after washing with a cell-saving device, is not unreasonable as a means of blood conservation. (Level of evidence C)	IIb
Postoperative mediastinal shed blood reinfusion using washed mediastinal blood (cell saving) is not unreasonable for blood conservation when used in conjunction with other blood conservation interventions. Washing of shed mediastinal blood may decrease lipid emboli and 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
Retrograde autologous priming of the CPB circuit is not unreasonable for blood conservation. (Level of evidence B)	IIb
Use of modified ultrafiltration is not unreasonable for blood conservation during CPB in pediatric patients or in patients for whom the priming volume is a very significant fraction of the total blood volume. (Level of evidence B)	IIb
Topical sealants used to assist in the repair of complex high-risk cardiac and aortic procedures are not unreasonable to limit bleeding in certain key situations (eg, left ventricular free wall rupture and aortic dissection) but are associated with complications that may limit their usefulness in less high risk situations. (Level of evidence C)	IIb
Screening preoperative bleeding time is not unreasonable 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 are not unreasonable for blood conservation if operation is planned within 24 hours. (Level of evidence C)	IIb

care testing used. At least one study strongly suggests that it is the multimodality approach that is important rather than the individual components of the process [530]. Table 7 lists the evidence-based recommendations that make up a multimodal approach to blood conservation. It is impossible to assign importance to each individual variable in Table 7, and it is possible that the end result of these interventions on blood conservation is greater than the sum of the parts. Nontheless, available evidence supports the use of transfusion algorithms and point-of-care tests to guide transfusion behavior and enhance blood conservation.

8) Summary Treatment Strategy—the TQM Approach

Class IIa

1. Total quality management (TQM), 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)

Several threads of evidence support the notion that a multifaceted approach to blood conservation produces the best results. This approach combines key features of preoperative assessment to identify high-risk patients along with perioperative modifications and the total support of participating health care providers with common goals of limiting postoperative bleeding and blood transfusion. Assuming that a multimodality approach can be achieved in a given institution, is that enough? How does one assess the adequacy of interventions? An important part of blood conservation is ongoing assessment of various interventions that are used at a given institution. This is important because of the random and nonrandom variations that may result from blood conservation interventions resulting in different outcomes at different institutions.

Continuous assessment of quality improvement has been termed "total quality management" (TQM). Blumenthal and Scheck [660] list four major elements of a TQM project: (1) cohort of similar patients, (2) a stable process of care, (3) a set of prioritized outcomes, and (4) an integrated measurement and analysis system. It is the fourth part of these criteria that fails in most TQM

endeavors. The evidence is mostly available to limit blood transfusion after cardiac procedures (ie, there is a cohort of similar patients with prioritized outcomes). Most institutions have already implemented many of the evidence-based blood conservation mechanisms (ie, stable process of care). The part that is lacking in ultimately reducing bleeding and blood transfusion is the "measurement and analysis" of which interventions are important at a given institution. A complete data system is often lacking in blood conservation. Collecting outcomes data on admission and discharge hematocrit, blood loss and blood product transfusion, and reoperation for bleeding is essential. Accurate risk adjustment using various risk factors (eg, surgeon, operation, age, sex, body surface area, and so forth) complements this data analysis. Quality improvement employs the triad of accurate outcomes measurement, thorough risk adjustment, and identifying the impact of the various blood conservation interventions on risk-adjusted outcomes. The TQM process must be viewed as an ongoing process that continually adjusts interventions consistent with improvement in blood transfusion practices. Most importantly, this requires active participation of all members of the health care team [661].

As an example, one successful set of innovative TQM studies was carried out by the Northern New England Cardiovascular Disease Study Group [662–665]. These investigators used a risk-adjustment scheme to predict mortality in patients undergoing CABG at five different institutions. After risk stratification, significant variability existed among the different institutions and providers. Statistical methods suggested that the variation in mortality rate was nonrandom (ie, "special variability" in the TQM vernacular). A peer-based, confidential TQM project addressed this variability and attempted to improve outcomes in the region. To study this nonrandom variability, representatives from each institution visited all institutions and reviewed the processes involved in performing CABG. Surgical technique, communication among providers, leadership, decision making, training levels, and environment were assessed at each institution. Significant variation among many of the processes was observed, and attempts to correct deficiencies were undertaken at each institution. Subsequent publications from these authors suggest that this approach improves outcomes for all providers at all institutions [666, 667]. Preliminary evidence suggests that this collaborative, peer-based, confidential TQM approach results in a decrease in operative mortality and, importantly, that providers who were outliers for risk-adjusted operative mortality were able to correct deficiencies and improve operative outcomes. Each of the practitioners in the five hospitals had implemented what they thought were high-quality interventions in CABG patients before beginning the TQM intervention. It was not until actual measurement of the process of care occurred that significant variability was noted and steps were taken to decrease this variability. A similar TQM process was undertaken for blood conservation at the New York Hospital with similar results [438]. Likewise, a compara-

ble TQM process improved the quality of care in patients undergoing percutaneous coronary interventions at another institution [668]. This type of TQM approach to blood conservation is viewed as the final common pathway for applying evidence-based information to blood conservation.

9) Summary

Based on available evidence, institution-specific protocols should screen for high-risk patients, as blood conservation interventions are likely to be most productive in this high-risk subset. Available evidence-based blood conservation techniques include (1) drugs that increase preoperative blood volume (eg, erythropoietin) or decrease postoperative bleeding (eg, antifibrinolytics), (2) devices that conserve blood (eg, intraoperative blood salvage and blood-sparing interventions), (3) interventions that protect the patient's own blood from the stress of operation (eg, autologous predonation and normovolemic hemodilution), (4) consensus, institution-specific blood transfusion algorithms supplemented with point-of-care testing, and most importantly (5) a multimodality approach to blood conservation combining all of the above supplemented with a TQM approach to the measurement and analysis of all blood conservation interventions used.

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Appendix 1

Authors' Financial Relationships With Industry

Author	Disclosure	Lecture Fees, Consultant, Paid Work	Research Grant Support
V.A. Ferraris	Yes	AstraZeneca, Aventis, Bayer, Network for Advancement of Transfusion Alternatives (NATA), and The Medicines Company	American Heart Association, Aventis, Bayer, BioMarin Pharma, Guilford, Medtronic, National Heart, Lung and Blood Institute, and The Medicines Company
S.P. Ferraris	No		
S.P. Saha	No		
E.A. Hessel	No		
C.K. Haan	No		
B.D. Royston	Yes	Azko Nobel, Bayer, GSK, Johnson & Johnson Pharmaceuticals	Bayer, Department of Health (UK), Fresenius, Inotherapeutics, National Blood Service (UK)
C.R. Bridges	Yes	Bayer	
R.S.D. Higgins	No		
G.J. Despotis	Yes	Bayer, Dyax, Inspire, Medtronic	Medtronic
J.R. Brown	No		
B.D. Spiess	Yes	Bayer, The Medicines Company	Bayer, Synthetic Blood International
L. Shore-Lesserson	Yes	Bayer, NovoNordisk	Bayer
M. Stafford-Smith	No		
C.D. Mazer	Yes	Bayer, NovoNordisk	Physician Services Inc (PSI) and Canadian Institutes of Health Research (CIHR)
E. Bennett-Guerrero	No		
S.E. Hill	Yes	Bayer, HemoConcepts	
S. Body	No		

Appendix 2

Methods Used in Guideline Development

1. Appointment of Blood Conservation Guideline Task Force Members

a. The Guideline Writing Group

The Chairman of the Blood Conservation Writing Group (VAF) was appointed by the Evidence-based Workforce of The Society of Thoracic Surgeons. The Writing Group Chairman appointed the Writing Group from among volunteers, some of whom were recruited from members of the Workforce. Other members of the Writing Group were recruited from a pool of surgeons and anesthesiologists with a known interest in blood conservation and blood transfusion. Writing Group members were recruited for their interests in blood conservation as well as their willing-ness to devote long hours to research and synthesis of information on various blood conservation topics. The Writing Group was charged by the STS Evidence-based Workforce with generating a complete document on blood conservation for review by others. Oversight of the Writing Group was the responsibility of the Operating Board of the STS Council on Quality, Research and Patient Safety (Richard P. Anderson, Chair) and by the STS Executive Committee.

b. The Guideline Review Group

After a draft of the complete guideline was created, the Society of Cardiovascular Anesthesia (SCA) was approached about participation in the guideline review process. A lead anesthesiologist of the SCA review group (BDS) was chosen by the Executive Committee of the SCA, and the lead reviewer picked acknowledged expert anesthesiologists in the field of blood conservation to help with the review of the rough draft of the blood conservation guidelines. Comments and critiques from the Review Group of the SCA are included in the final blood conservation document.

2. Conduct of the Literature Search and Document Development

The lead author of the guideline (VAF) developed an outline for the document and assigned topics in the outline to each member of the STS Writing Group. Each Writing Group member performed an exhaustive search of available literature on their assigned topic. The Writing Group members used the following strategy for accumulating available evidence. First, a complete search of the published literature was essential. Often this involved searching many public access information sources, including MEDLINE (www.ncbi.nlm.nih.gov/entrez), EMBASE (www.embase.com), CINAHL (www.cinahl.com), and the Cochrane Collaboration (www.cochrane.org) for reports published in the peer-reviewed and non–peer-reviewed medical literature. Search of these databases using keywords relating to the assigned topic generated a list of relevant references. Each Writing Group member synthesized an evidence-based narrative and recommendation based on these references and on other information sources.

Second, all types of information sources were considered in summarizing available evidence. One has to realize that only about one third of the world's medical literature appears on large computer databases such as MEDLINE. Computerized databases such as MEDLINE are incomplete, especially in areas of subspecialization like cardiothoracic surgery. For complete review of the medical literature on a particular assigned subject, each Writing Group author was encouraged to conduct an exhaustive search of all available literature, not only Web-based computer databases like MEDLINE, but also unpublished trials and so-called "fugitive literature" (government reports, proceedings of conferences, published PhD theses, industry sponsored studies, and so forth).

Traditionally, there is a hierarchy among information sources with more weight given to more rigorous studies such as RCTs and systematic reviews (eg, meta-analyses) than to observational studies or to case reports. Because of this hierarchy, many investigators ignore other sources that may provide useful information. Each Writing Group member was charged with understanding the following hierarchy of information sources, in order of descending importance: randomized controlled trials (RCTs), systematic reviews (eg, meta-analyses), observational studies (eg, case-control or cohort studies), fugitive literature (government reports, proceedings of conferences, published PhD theses, unpublished negative randomized trials, and so forth), case reports, expert consensus, and internet sources. Although this hierarchy is pseudoscientific, RCTs are usually considered the only means of proving cause and effect of a given intervention, but a propensity adjusted observational study may provide similar information [764, 755]. There is some evidence that well-done observational studies give results comparable to RCTs dealing with similar outcomes [756, 757]. Likewise, information retrieved from the "fugitive" literature (eg, unpublished negative randomized trials) may provide useful information for summary analysis that might otherwise be ignored in a literature search. Each Writing Group author was encouraged to search all of the information sources in the hierarchy, as each might contribute important information and none should be ignored.

Each member of the STS Writing Group was encouraged to summarize numerous RCTs using meta-analysis where appropriate. If several RCTs with similar endpoints and with homogeneous research groups appeared in the literature search, then meta-analysis was performed. Two of the Writing Group members with biostatistical experience (VAF and BDR) reviewed all guideline content for statistical rigor, especially the meta-analyses.

3. Peer Review and Oversight by Professional Societies

After completion of the final draft by the STS Writing Group and after review by the SCA Review Group, the revised document was disseminated to all members of the STS and the SCA electronically. The lead author (VAF) compiled the comments from this peer-based review and added them to the final document where appropriate. After this peer-based review, the final document was again circulated to the Writing Group and the Review Group for final approval. After majority concurrence by the Writing Group and the Review Group, the final document was reviewed by the Executive Committee of the STS. Only after this final review was the manuscript submitted to *The Annals of Thoracic Surgery*. The manuscript was then subjected to the usual peer-review process of the *The Annals*, and the reviewers' comments were added to the revised manuscript where appropriate.

4. Recommendations of the Writing Group and the Review Group

Each member of the Writing Group and the Review Group evaluated the final document with all recommendations and classifications of level of evidence, using the classification scheme in Table 1. Each Writing Group and Review Group member voted on the final recommendations and the final vote talley appears in the following spreadsheet (Appendix 2, Table 1).

Appendix 2, Table 1. Final Voting on Recommendations by Writing Group and Review Group Members (n = 17)

Recommendation	Class	Yes	No	Reason(s) for disagreement
Preoperative identification of high-risk patients (advanced age, preoperative anemia, small body size, non–coronary artery bypass graft surgery (CABG) 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 because they account for the majority of blood products transfused. (Level of evidence A)	I	17	0	
High-dose aprotinin is indicated to reduce the number of patients requiring blood transfusion, to reduce total blood loss, and to limit reexploration in high-risk patients undergoing cardiac operations. Benefits of use should be balanced against the increased risk of renal dysfunction. (Level of evidence A)	I	15	2	Concerned about renal safety issues—should add qualifying statement.
Low-dose aprotinin is indicated to reduce the number of patients requiring blood transfusion and to reduce the total blood loss in patients having cardiac procedures. (Level of evidence A)	I	15	2	No safety data.
Lysine analogues like epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) are indicated to reduce the number of patients who require blood transfusion, and to reduce total blood loss after cardiac operations. These agents are slightly less potent blood-sparing drugs and the safety profile of these drugs is less well studied compared with aprotinin. (Level of evidence A)	I	16	1	Should be class IIb because of limited safety data.
Routine use of red-cell saving is helpful for blood conservation in cardiac operations using cardiopulmonary bypass (CPB), except in patients with infection or malignancy. (Level of evidence A)	I	17	0	
Preoperative hematocrit and platelet count are indicated for risk prediction, and abnormalities in these variables are amenable to intervention. (Level of evidence A)	I	17	0	
A multimodality 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 will limit blood transfusion and provide optimal blood conservation for cardiac operations. (Level of evidence A)	I	17	0	
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	17	0	
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	17	0	
Routine prophylactic use of desmopressin acetate (DDAVP) is not recommended to reduce bleeding or blood transfusion after cardiac operations using CPB. (Level of evidence A)	III	17	0	
Use of prophylactic positive end-expiratory pressure (PEEP) to reduce bleeding postoperatively is not effective. (Level evidence B)	III	17	0	
Routine use of intraoperative platelet or plasmapheresis is not recommended for blood conservation during cardiac operations using CPB. (Level of evidence A)	III	17	0	
Leukocyte filters on the CPB circuit for leukocyte-depletion should not be used for perioperative blood conservation and may actually activate leukocytes during CPB. (Level of evidence B)	III	16	1	Leukoreduction may be helpful for other things besides blood conservation.
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	16	1	May replace red cell mass in excessive bleeding.
Routine use of ultrafiltration during or immediately after CPB is not helpful for blood conservation in adult cardiac operations. (Level of evidence B)	III	15	2	May have small but significant effect.
Topical hemostatic agents that employ bovine thrombin are not helpful for blood conservation during CPB and may be potentially harmful. (Level of evidence B)	III	17	0	
Preoperative screening of the intrinsic coagulation system is not recommended unless there is a clinical history of bleeding diathesis. (Level of evidence B)	III	16	1	Useful but low yield.
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	15	2	Concerned that new viral or other infectious agents will change this recommendation.

Appendix 2, Table 1. Final Voting on Recommendations by Writing Group and Review Group Members (n = 17) (Continued)

Recommendation	Class	Yes	No	Reason(s) for disagreement
Patients who have thrombocytopenia (less than 50,000/mm^2), who are hyperresponsive to aspirin or other anti-platelet 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 for these high-risk patients. (Level of evidence B)	IIa	17	0	
It is reasonable to discontinue thienopyridines 5 to 7 days before cardiac procedures to limit blood loss and transfusion. Failure to discontinue these drugs before operation risks increased bleeding and possibly worse outcome. Caution must be used with sudden withdrawal of antiplatelet therapy in the presence of drug-eluting stents. This can lead to stent thrombosis and the surgical team should consider various alternatives to maintain stent patency. That could even include hospitalization to convert thienopyridine therapy to short-acting GP2b/3a inhibitors for a few days before operation. (Level of evidence B)	IIa	17	0	
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	15	2	Should be class IIb because of too many other conflicting data and possibility that preoperative aspirin is protective.
With hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable, as 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	17	0	
It is reasonable to transfuse non–red 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	17	0	
During cardiopulmonary bypass with moderate hypothermia, transfusion of red cells for a hemoglobin level ≤ 6 g/dL is reasonable except in patients at risk for decreased cerebral oxygen delivery (ie, history of cerebrovascular accident, diabetes mellitus, cerebrovascular disease, carotid stenosis) where higher hemoglobin levels may be justified. (Level of evidence C)	IIa	17	0	
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 variables (eg, hematocrit, SVO$_2$, electrocardiographic or echocardiographic evidence of myocardial ischemia, etc). (Level of evidence C)	IIa	17	0	
In patients after cardiac operations with hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable and can be life-saving. Transfusion of red cells is reasonable in most postoperative patients with hemoglobin ≤ 7 g/dL, but no high-level evidence supports this recommendation. (Level of evidence C)	IIa	17	0	
It is reasonable to transfuse non–red 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	17	0	
Recombinant human erythropoietin (EPO) is reasonable to restore red blood cell volume in patients undergoing autologous preoperative blood donation before cardiac procedures. However, no large-scale safety studies for use of this agent in cardiac surgical patients have been performed. Available evidence suggests an acceptable safety profile. (Level of evidence A)	IIa	13	4	Should be class IIb because of limited safety data. Predonation is frequently impractical and has low efficacy. The use of a high-cost drug that does not have good evidence to augment a low-efficacy procedure is unwarranted (class III).

Appendix 2, Table 1. Final Voting on Recommendations by Writing Group and Review Group Members (n = 17) (Continued)

Recommendation	Class	Yes	No	Reason(s) for disagreement
Recombinant human EPO is a reasonable alternative for anemic low-risk elective patients (hemoglobin ≤13 g/dL) before cardiac procedures, provided that EPO is given in conjunction with iron therapy several days or more before operation. (Level of evidence B)	IIa	16	1	Needs several weeks, not days (not practical).
Predonation of as much as two units of autologous blood is reasonable for blood conservation in carefully selected (mostly elective) patients before routine cardiac operation, particularly when coupled with appropriately dosed EPO therapy and/or iron therapy. (Level of evidence A)	IIa	14	3	Should be class IIb because of limited safety data. Predonation is frequently impractical and has low efficacy. The use of a high-cost drug that does not have good evidence to augment a low-efficacy procedure is unwarranted (class III).
Off-pump coronary artery bypass (OPCAB) is a reasonable means of blood conservation, provided that emergent conversion to on-pump bypass is unlikely either based on surgeon experience or patient characteristics. (Level of evidence A)	IIa	16	1	Only recommendation that is dependent on technical skill. Not a recommendation for every program, only those with appropriate technical skills.
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	16	1	Alternatives are not reliable enough.
A comprehensive, integrated, multimodality blood conservation program in the intensive care unit is a reasonable means to limit blood transfusion. (Level of evidence B)	IIa	17	0	
Total quality management (TQM), 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	17	0	
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 activators, streptokinase) are associated with increased bleeding after cardiac operations. It is not unreasonable to stop these medications before operation 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 a notable exception in that it is the only agent that may be discontinued shortly before operation or not at all. (Level of evidence C)	IIb	16	1	Too broad of a category.
It is not unreasonable 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	16	1	Not enough data.
In patients on CPB with risk for critical end-organ ischemia/injury, it is not unreasonable to keep the hemoglobin level ≥7 g/dL. (Level of evidence C)	IIb	16	1	Evidence does not justify this recommendation.
It is not unreasonable to use preoperative EPO, given at least a few days before operation, to increase red cell mass in elective patients who are at risk for postoperative anemia and depressed endogenous EPO production. (Level of evidence C)	IIb	17	0	
Use of DDAVP is not unreasonable 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	17	0	

Appendix 2, Table 1. Final Voting on Recommendations by Writing Group and Review Group Members (n = 17) (Continued)

Recommendation	Class	Yes	No	Reason(s) for disagreement
Use of recombinant factor VIIa concentrate is not unreasonable for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB. (Level of evidence B)	IIb	16	1	Should be class III until more safety and efficacy data are available.
A trial of therapeutic PEEP to reduce excessive postoperative bleeding is not unreasonable. (Level of evidence B)	IIb	15	2	Does not believe that evidence is compelling enough.
It is not unreasonable to use open venous reservoir membrane oxygenator systems during cardiopulmonary bypass for reduction in blood utilization and improved safety. (Level of evidence C)	IIb	14	3	Closed venous system is safer and better for blood conservation based on personal observation. Need to separate type of reservoir from type of oxygenator.
All commercially available blood pumps provide acceptable blood conservation during CPB. It is not unreasonable to prefer centrifugal pumps because of perfusion safety features. (Level of evidence B)	IIb	16	1	Centrifugal pumps are standard of care.
For patients requiring longer CPB times (more than 2–3 hours), it is not unreasonable to consider maintenance of higher or patient-specific heparin concentrations during CPB to reduce hemostatic system activation, reduce consumption of platelets and coagulation proteins, and reduce blood transfusion. (Level of evidence B)	IIb	16	1	Not necessary.
It is not unreasonable to 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 to reduce bleeding and blood transfusion requirements. (Level of evidence B)	IIb	16	1	Not enough data.
Heparin-coated bypass circuits (either the oxygenator alone or the entire circuit) are not unreasonable for blood conservation in cardiac operations. (Level of evidence B)	IIb	17	0	
Low doses of systemic heparinization (activated blood clotting time ~300 s) are not unreasonable for blood conservation during CPB, but the possibility of underheparinization and other safety concerns have not been well studied. (Level of evidence B)	IIb	17	0	
It is not unreasonable to use low prime and minimized extracorporeal bypass circuits to reduce the fall in hematocrit during CPB as part of a multimodality blood conservation program. (Level of evidence B)	IIb	16	1	May cause too much hemoconcentration with resultant renal impairment from nonpulsatile flow.
Acute normovolemic hemodilution is not unreasonable for blood conservation but its usefulness is not well established. It could be utilized as part of a multipronged approach to blood conservation. (Level of evidence B)	IIb	16	1	It is a very low efficacy procedure with no supporting evidence.
During CPB, it is not unreasonable to use intraoperative autotransfusion, either with blood directly from cardiotomy suction or recycled using a cell-saving device, to augment blood conservation. (Level of evidence C)	IIb	16	1	May have some harmful CNS effects.
Shortly after the completion of cardiopulmonary bypass, salvage of pump blood, either administered without washing or after washing with a cell-saving device, is not unreasonable as a means of blood conservation. (Level of evidence C)	IIb	16	1	Discard of available fresh autologous whole blood is intuitively wrong as part of a multimodality approach.
Postoperative mediastinal shed blood reinfusion using washed mediastinal blood (cell saving) is not unreasonable for blood conservation when used in conjunction with other blood conservation interventions. Washing of shed mediastinal blood may decrease lipid emboli and 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	15	2	May be helpful for blood conservation but harmful for proinflammatory effects. Not enough safety data.

Appendix 2, Table 1. Final Voting on Recommendations by Writing Group and Review Group Members (n = 17) (Continued)

Recommendation	Class	Yes	No	Reason(s) for disagreement
Retrograde autologous priming of the CPB circuit is not unreasonable for blood conservation. (Level of evidence B)	IIb	15	2	Should be class IIa according to available data as cited. No safety data, and may cause harm (class III recommendation).
Use of modified ultrafiltration is not unreasonable for blood conservation during CPB in pediatric patients or in patients for whom the priming volume is a very significant fraction of the total blood volume. (Level of evidence B)	IIb	16	1	Do not feel that data supports this recommendation.
Topical sealants used to assist in the repair of complex high-risk cardiac and aortic procedures are not unreasonable to limit bleeding in certain key situations (eg, left ventricular free wall rupture and aortic dissection) but are associated with complications that may limit their usefulness in less high risk situations. (Level of evidence C)	IIb	16	1	Should not replace good surgical technique.
Screening preoperative bleeding time is not unreasonable in high-risk patients, especially those who receive preoperative antiplatelet drugs. (Level of evidence B)	IIb	14	3	Bleeding time is not available and is not recommended for screening purposes by other professional organizations. Identification of a high-risk patient is adequate. Bleeding time will not usefully subdivide this high-risk group into either a lower risk group, or into an even higher risk group.
Devices aimed at obtaining direct hemostasis at catheterization access sites are not unreasonable for blood conservation if operation is planned within 24 hours. (Level of evidence C)	IIb	16	1	Not enough data to support recommendation.