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SPECIAL ARTICLE

Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory for Management of Perioperative Bleeding and Hemostasis in Cardiac Surgery Patients

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Bleeding after cardiac surgery is a common and serious complication leading to transfusion of multiple blood products and resulting in increased morbidity and mortality. Despite the publication of numerous guidelines and consensus statements for patient blood management in cardiac surgery, research has revealed that adherence to these guidelines is poor, and as a result, a significant variability in patient transfusion practices among practitioners still remains. In addition, although utilization of point-of-care (POC) coagulation monitors and the use of novel therapeutic strategies for perioperative hemostasis, such as the use of coagulation factor concentrates, have increased significantly over the last decade, they are still not widely available in every institution. Therefore, despite continuous efforts, blood transfusion in cardiac surgery has only modestly declined over the last decade, remaining at ≥50% in high-risk patients. Given these limitations, and in response to new regulatory and legislature requirements, the Society of Cardiovascular Anesthesiologists (SCA) has formed the Blood Conservation in Cardiac Surgery Working Group to organize, summarize, and disseminate the available best-practice knowledge in patient blood management in cardiac surgery. The current publication includes the summary statements and algorithms designed by the working group, after collection and review of the existing guidelines, consensus statements, and recommendations for patient blood management practices in cardiac surgery patients. The overall goal is creating a dynamic resource of easily accessible educational material that will help to increase and improve compliance with the existing evidence-based best practices of patient blood management by cardiac surgery care teams. (Anesth Analg 2019;129:1209–21)

GLOSSARY

A10 = amplitude at 10 minutes; **ACT** = activated clotting time; **ANH** = acute normovolemic hemodilution; **AT** = antithrombin; **ATACAS** = Aspirin and Tranexamic Acid for Coronary Artery Surgery; **CPB** = cardiopulmonary bypass; **CPI** = Continuous Practice Improvement; **CT** = clotting time; **DAPT** = dual antiplatelet therapy; **DDAVP** = 1-deamino-8-D-arginine vasopressin; **EACA** = ε-aminocaproic acid; **ECMO** = extra corporeal membrane oxygenation; **EPO** = erythropoietin; **EXTEM** = extrinsic pathway thromboelastometry; **FF** = functional fibrinogen; **FFP** = fresh-frozen plasma; **FIBTEM** = fibrinogen-based thromboelastometry; **Hb** = hemoglobin; **HEPTEM** = heparinase thromboelastometry; **HIT** = heparin-induced thrombocytopenia; **hTEG** = heparinase thromboelastography; **iCA^{++}** = ionized calcium; **INR** = international normalized ratio; **INTEM** = intrinsic pathway thromboelastometry; **LY30** = clot lysis at 30 minutes; **MA** = maximum amplitude; **ML** = maximum lysis; **$P2Y_{12}$** = platelet receptor $P2Y_{12}$; **PCC** = prothrombin complex concentrate; **PF24** = plasma frozen within 24 hours after phlebotomy; **PLT** = platelet; **POC** = point of care; **R** = reaction time; **RBC** = red blood cell; **RCT** = randomized controlled trial; **REPLACE** = Randomized Evaluation of Fibrinogen versus Placebo in Complex Cardiovascular Surgery; **rFVIIa** = recombinant activated factor VII; **ROTEM** = rotational thromboelastometry; **RV** = right ventricle; **SCA** = Society of Cardiovascular Anesthesiologists; **STS** = Society of Thoracic Surgeons; **T** = temperature; **TEG** = thromboelastography; **TRICS** = Transfusion Requirements in Cardiac Surgery; **TXA** = tranexamic acid

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Coagulopathy associated with cardiac surgery is a multifactorial serious complication that may result in massive bleeding requiring transfusion of red blood cells (RBCs) and procoagulant products to obtain adequate hemostasis.[1,2]

The importance of blood conservation strategies in cardiac surgery is emphasized by the fact that cardiovascular surgical procedures have among the highest overall rate of RBC transfusion when compared to all other surgeries, accounting for 10%–15% of all RBC transfusions in the United States and the United Kingdom.[3,4] Furthermore, approximately 10% of all cardiac surgery patients suffer from severe or massive blood loss, and up to 5% of all patients having cardiac surgery require emergent reexploration in an attempt to correct ongoing bleeding and establish adequate hemostasis.[2,5]

A significant body of evidence associates allogeneic blood transfusions during cardiac surgery with increased risk of serious postoperative morbidities including infections, atrial fibrillation, respiratory complications, acute kidney injury, and short-term and long-term mortality,[6–15] showing a dose–response relationship where morbidity and mortality are directly proportional to the number of units of RBC transfused.[8,14] Moreover, reduction of perioperative transfusion by initiation of blood management practices has been associated with decrease in major postoperative morbidity and mortality.[16–18]

Despite this evidence base, and the publication of numerous practice guidelines,[19–26] much confusion remains about the optimal management of perioperative bleeding in cardiac surgery patients.[5,27–30]

Data show that only a small fraction of published guidelines is successfully integrated into daily clinical practice.[31,32] As a specific example, publication of the 2011 update to the Society of Thoracic Surgeons (STS)/Society of Cardiovascular Anesthesiologists (SCA) Blood Conservation Guideline[19] did not result in a decrease in blood product utilization in cardiac surgery patients, most probably, due to a low rate of guidelines adoption by practitioners.[4,33] Furthermore, while recent STS reports[34,35] demonstrate a modest decline in blood product utilization in cardiac surgical procedures over the last decade, allogeneic blood transfusions still occur in over 50% of high-risk cardiac surgery patients.[3,4,27,36] In the recently published Transfusion Requirements in Cardiac Surgery (TRICS) III trial, for example, RBC transfusions occurred in 52.3% of the patients in the restrictive transfusion group and in 72.6% of the patients in the liberal transfusion group.[36] It is believed, however, that with the successful adoption and implementation of best-practice point of care (POC)–based transfusion algorithms, at least some of these transfusions could be potentially avoided.[37–41]

In response to recent changes in statutory regulations and to facilitate improvement in blood conservation and transfusion management in cardiac surgery, SCA formed a Continuous Practice Improvement (CPI) subcommittee. This subcommittee appointed a Blood Conservation In Cardiac Surgery Working Group—a panel of experts that was directed to organize and summarize the existing guidelines and consensus statements related to blood conservation in cardiac surgery. Additional information about the SCA CPI initiative and the various focus working groups can be found in a recent article and accompanying editorial by Muehlschlegel et al[42] and Schwann et al,[43] respectively.

The current report is the summary of recommendations for blood management in cardiac surgery, made by the SCA CPI Blood Conservation Working Group. This summary focuses on the perioperative management of adults undergoing cardiovascular surgery in which significant blood loss occurs or is expected. Excluded from this document are neonates, infants, children <18 years old, and adults weighing <40 kg.

The current summary of recommendations is not a set of new guidelines. They may be adopted, modified, or rejected according to clinical and institutional needs and constraints. Furthermore, practitioners will need to consider the clinical situation and exercise judgment in applying the more generalized recommendations contained herein. In addition, the recommendations included here are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome.

METHODS

Working Group

The SCA Blood Conservation Working Group includes appointed members from the United States and internationally. Efforts were made to select members who are experts in patient blood management both from private and academic cardiac anesthesia practices as well as representatives from international cardiac anesthesiology societies. The working group developed the current recommendations after reviewing existing guidelines and consensus statements as well as original published research studies from peer-reviewed journals. In addition, expert opinion about the recommendations was solicited from the task force members. All available information was used to build consensus within the working group to finalize the recommendations.

Search Strategy and Identification of Guidelines

The following databases were searched for relevant clinical studies from inception until October 30, 2018: MEDLINE (Ovid), EMBASE (Embase.com), PUBMED (NCBI), the Cochrane Central Register of controlled Trials (CENTRAL), BIOSIS (Web of Science), and Google Scholar. The search was not limited by date or publication status, but was restricted to articles that were only published in English. In addition, we also searched the reference lists of relevant reviews, available online conference proceedings, and published practice guidelines and their respective reference lists. Inclusion criteria included randomized controlled trials (RCTs), meta-analyses, large-scale

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observational studies, and practice guidelines of patients undergoing cardiovascular surgical procedures with or without cardiopulmonary bypass (CPB). Reviewers independently screened citations to select publications that met inclusion criteria. Studies were not blinded to author, journal, or institution. The specific search terms that were used in obtaining relevant publications are detailed in Supplemental Digital Content 1, Appendix 1, http://links.lww.com/AA/C902.

Agreement (defined as consensus of ≥75% of the members of the working group on a specific topic) was reached through conference calls and face-to-face meetings. When no agreement could be obtained, or in cases that guidelines papers lacked or differed in recommendations, a consensus was reached following a modified Delphi process.[44] Members who were unable to attend a face-to-face meeting voted via email. Three Delphi cycles were required to reach a consensus, and a final decision was made through a series of teleconference calls and electronic communications. In the absence of published evidence or cutoff values for transfusion triggers, expert consensus statements, based on the most updated published literature, were made to cover specific issues that are essential to daily practice. The level of evidence and the strength of the recommendations (when available) are reported as well (Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C903).

RESULTS

The literature search yielded a total of 892 titles that were identified and their abstracts reviewed, from which 213 relevant publications were fully reviewed by the working group. Out of the 213 reviewed publications, a final list of 9 practice guidelines was included for summary in the current publication: (1) "Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline"[26]; (2) "2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines"[19]; (3) "2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines"[45]; (4) "Management of Severe Perioperative Bleeding: Guideline from the European Society of Anaesthesiology"[20]; (5) The "Management of Severe Perioperative Bleeding: Guideline from the European Society of Anaesthesiology, first update 2016"[21]; (6) "Practice Guidelines for Perioperative Blood Management: an Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management"[22]; (7) "Platelet Transfusion: a Clinical Practice Guideline from the AABB"[23]; (8) "Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage"[24]; and (9) "2017 EACTS/EACTA Guidelines on Patient Blood Management for Adult Cardiac Surgery."[25]

Summary of recommendations for common daily practices, including preoperative management of anemia and platelet (PLT) function assessment when indicated, as well as intraoperative monitoring of hemostasis, transfusion of blood products, and administration of pharmacological adjuvants in cardiac surgical patients is presented in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C903. This summary is based on the most recent published blood management guidelines. In addition, a graphical best-practice advisory for the practicing clinician that can be used at the POC is also included. This graphical advisory includes a summary statement (Figure 1) and 2 separate practical algorithms: (1) an algorithm based on viscoelastic POC coagulation testing (Figure 2) and (2) an algorithm based on "conventional" laboratory coagulation tests when viscoelastic tests are unavailable (Figure 3).

DISCUSSION

In an attempt to minimize the existing gap between published guidelines and clinical practice patterns in blood conservation in cardiovascular surgery patients, the current publication is a summary of recommendations that creates a "best-practice" advisory that can be easily adopted by clinicians. This advisory contains a summary statement and 2 transfusion algorithms.

The algorithms are based on a stepwise escalating approach where complete heparin reversal using protamine is the first step. If excessive microvascular bleeding is present after heparin reversal, an assessment of PLTs and fibrinogen is required as well as evaluation for coagulation factors deficiency. It is also important to remember that CPB is associated with significant fibrinolysis,[46,47] and therefore, the use of antifibrinolytic agents[48–50] should be continued beyond the operating room, or restarted if already discontinued, in cases with excessive postoperative bleeding.[51,52]

Patients may require transfusion of a single component, but frequently >1 component is required to achieve adequate hemostasis. After each round of treatment, clinical assessment of bleeding as well as evaluation of hemoglobin (Hb) and of the coagulation system is needed to avoid unnecessary over transfusion. Regardless of the algorithm used, the practitioner must also correct general abnormal physiologic conditions that may contribute to coagulopathy such as hypothermia and acidosis.

The development and implementation of a successful blood management program in cardiovascular surgical patients is a joint effort that requires involvement of multiple stakeholders and should include cardiovascular surgeons, anesthesiologists, perfusionists, intensivists, blood bank transfusion experts, nursing staff, and hospital administrative and support staff. The recommendations presented here apply to patients undergoing cardiovascular surgical procedures with or without the use of CPB, where blood transfusions and/or other adjuvant hemostatic therapies are indicated. They are directly applicable to anesthesiologists, surgeons, intensivists, and other care providers who are involved in the perioperative care of these patients.

The rationale for recommendations for essential common daily practices for blood conservation in cardiac surgical patients is presented in the following sections.

Preoperative Hb Optimization

Preoperative anemia (defined by the World Health Organization as an Hb level <12.0 g/dL in women and <13.0 g/dL in men) is present preoperatively in 25%–30% of cardiac surgery patients[53] and is a strong predictor for perioperative transfusion of allogeneic blood products.[54–56] It is recommended that patients be assessed for preoperative

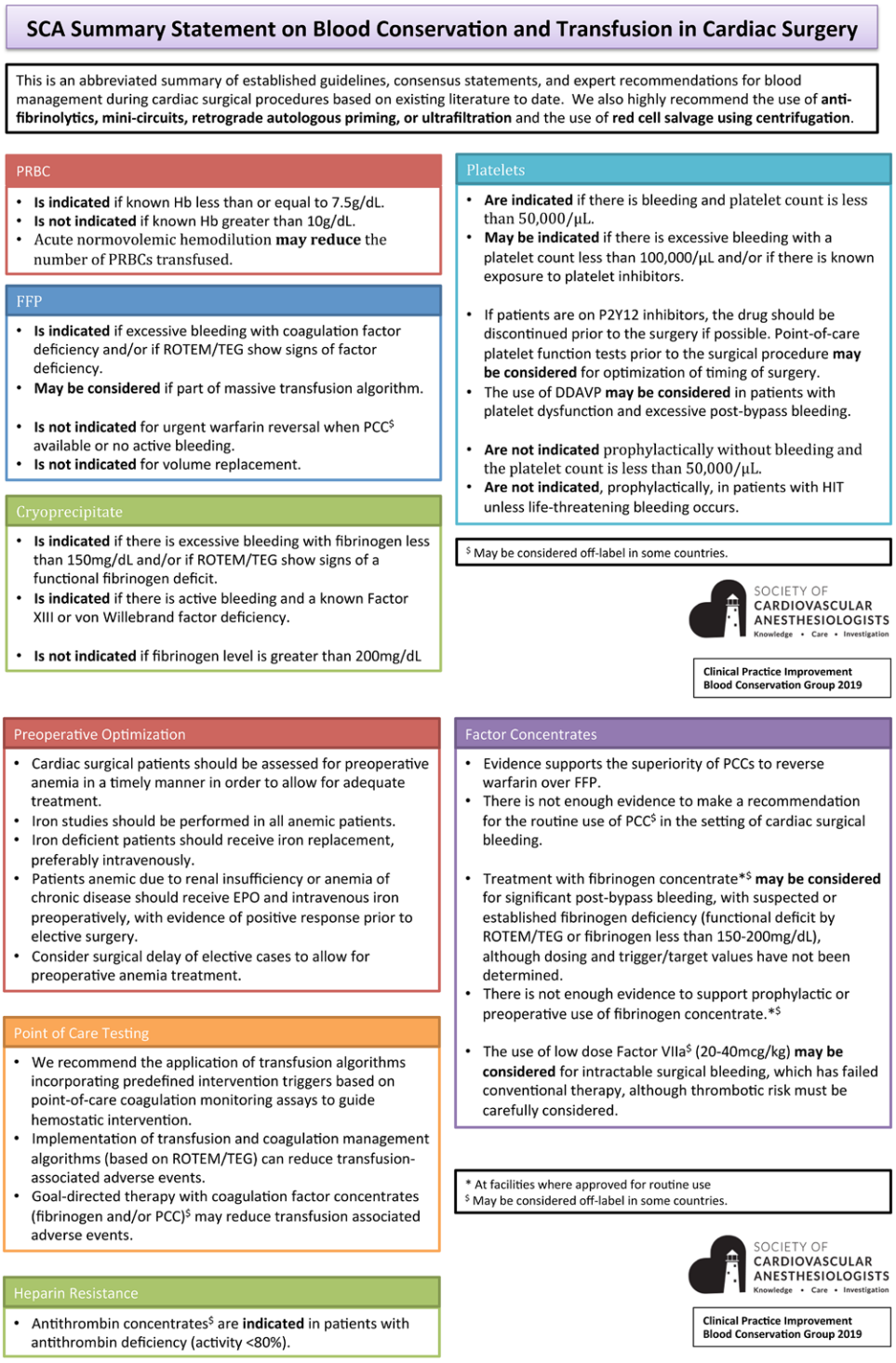

Figure 1. SCA Summary Statement on Blood Conservation and Transfusion in Cardiac Surgery. EPO indicates erythropoietin; FFP, fresh-frozen plasma; PCC, prothrombin complex concentrate; ROTEM, rotational thromboelastometry; SCA, Society of Cardiovascular Anesthesiologists; TEG, thromboelastography.

anemia several weeks before elective surgery to provide sufficient time for therapy, if needed.[20,21] Though studies are somewhat inconclusive regarding the efficacy of iron supplementation before cardiac surgery,[57,58] there is a strong agreement that supplemental iron is effective in patients with iron deficiency anemia. Therefore, existing guidelines do recommend preoperative iron therapy for patients with iron deficiency anemia. Erythropoietin with or without iron is recommended for patients with noniron deficiency anemia (renal failure, anemia of chronic disease, etc) or in patients who refuse blood transfusions.[19–22,25] Prophylactic RBC transfusion in asymptomatic anemic patients, before surgery, is not recommended.[19–22,24,25]

Heparin Resistance and Antithrombin Administration

Heparin resistance or altered heparin responsiveness is the inability to reach a target activated clotting time, despite

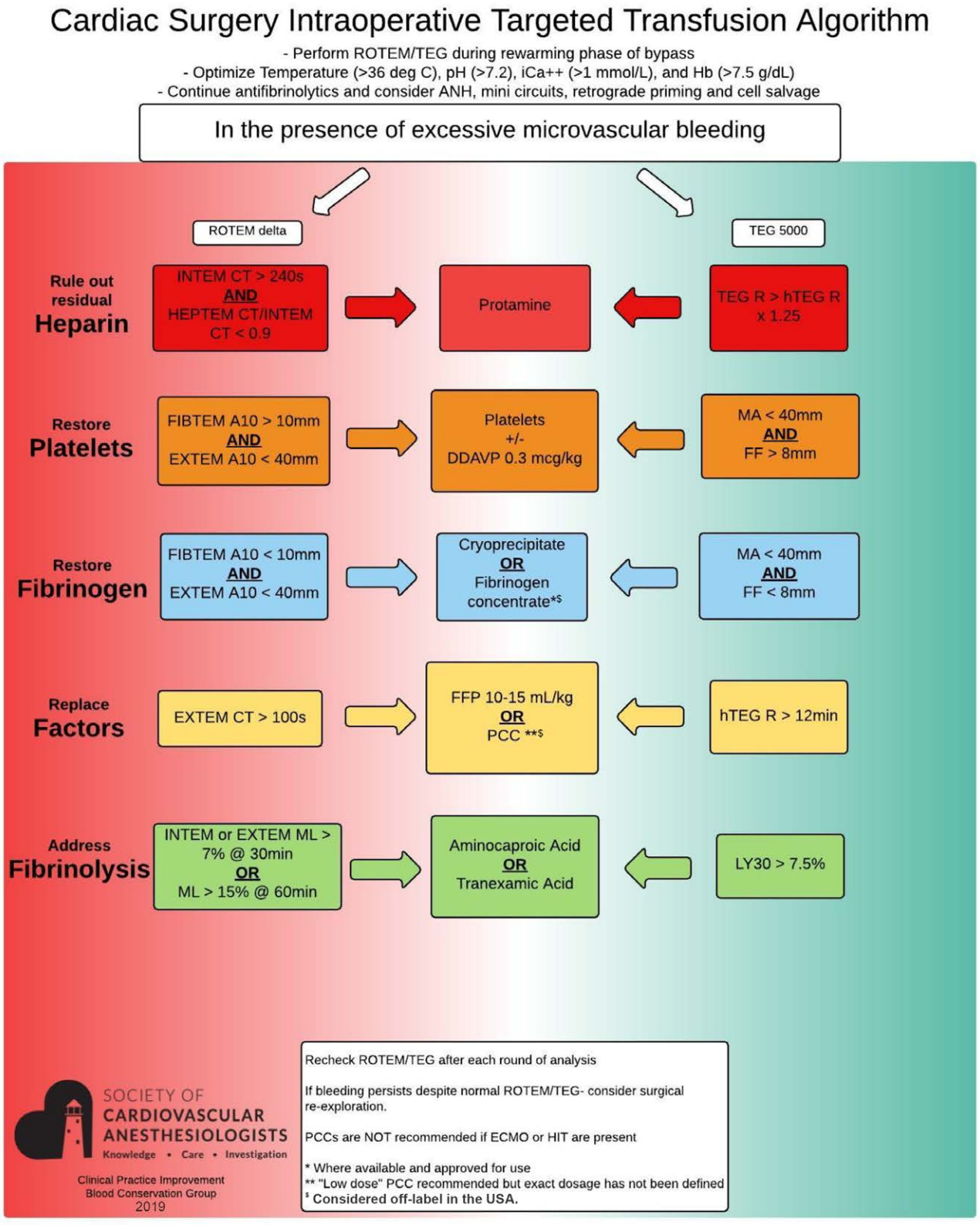

Figure 2. SCA ROTEM/TEG-based cardiac surgery intraoperative transfusion algorithm. ANH indicates acute normovolemic hemodilution; A10, amplitude at 10 minutes; CT, clotting time; DDAVP, 1-deamino-8-D-arginine vasopressin; ECMO, extra corporeal membrane oxygenation; EXTEM, extrinsic pathway thromboelastometry; FIBTEM, fibrinogen-based thromboelastometry; FF, functional fibrinogen; FFP, fresh-frozen plasma; Hb, hemoglobin; HEPTEM, heparinase thromboelastometry; HIT, heparin-induced thrombocytopenia; hTEG, heparinase thromboelastography; iCA^{++}, ionized calcium; INTEM, intrinsic pathway thromboelastometry; LY30, clot lysis at 30 min; MA, maximum amplitude; ML, maximum lysis; PCC, prothrombin complex concentrate; R, reaction time; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

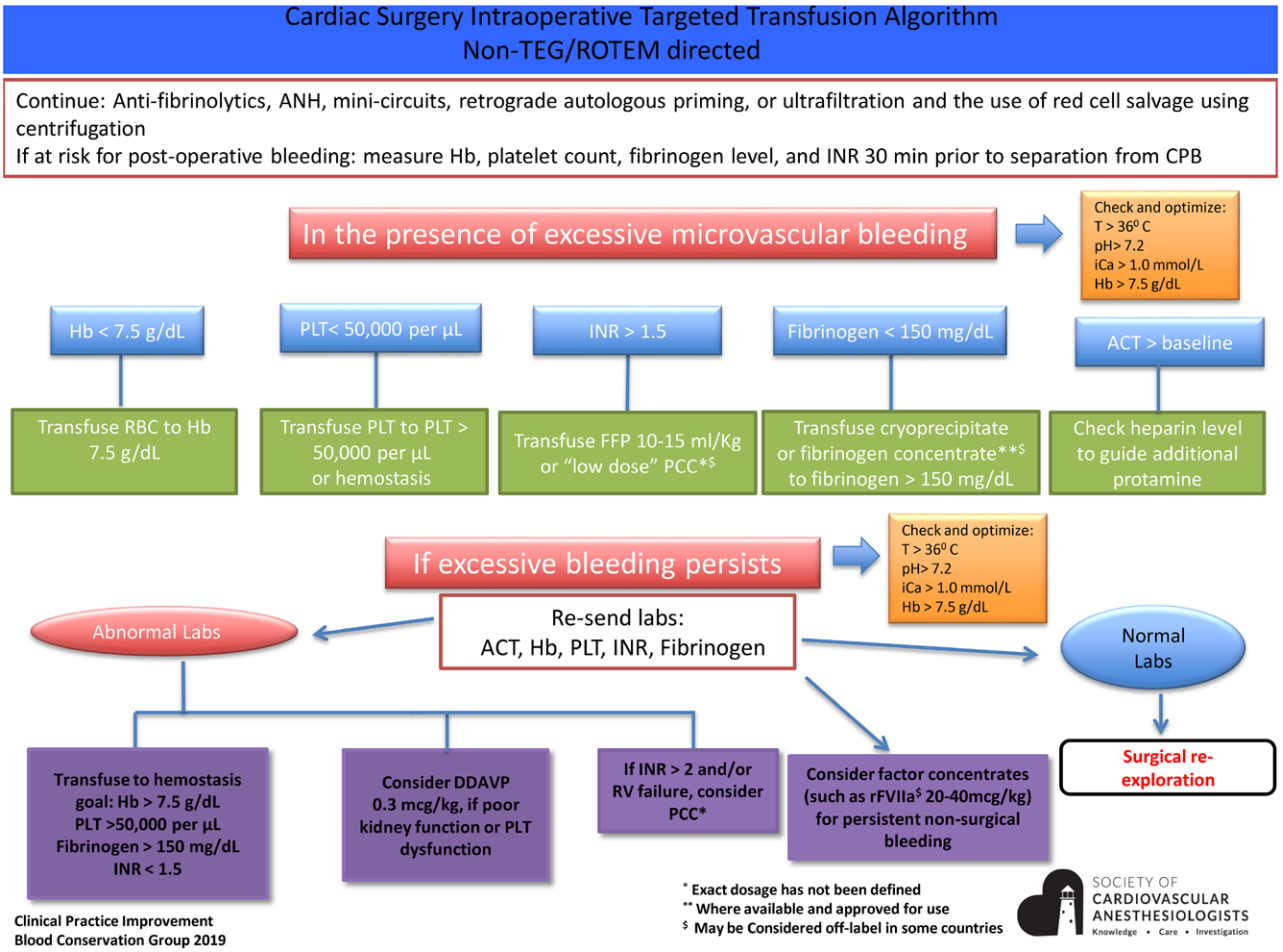

Figure 3. SCA non-ROTEM/TEG-based cardiac surgery intraoperative transfusion algorithm. ACT indicates activated clotting time; ANH, acute normovolemic hemodilution; CPB, cardiopulmonary bypass; DDAVP, 1-deamino-8-D-arginine vasopressin; FFP, fresh-frozen plasma; Hb, hemoglobin; iCA^{++}, ionized calcium; INR, international normalized ratio; PCC, prothrombin complex concentrate; PLT, platelets; RBC, red blood cell; rFVIIa, recombinant activated factor VII; RV, right ventricle; T, temperature.

administration of an adequate heparin dose. Patients resistant to heparin, mainly in the context of preoperative heparin infusion, may have low levels of antithrombin (AT).[59] This may result in inability to achieve adequate anticoagulation or may require higher than predicted doses of heparin to do so. Furthermore, with repeated heparin doses, it is not uncommon to require higher than predicted doses of protamine to reverse the effects of heparin after CPB, exposing the patient to potential protamine overdose and the associated possible complications. To avoid this, supplementation of AT before CPB (although considered off-label in the United States) may restore AT levels, improve heparin sensitivity, and assist in establishing adequate anticoagulation.[60–62] Prophylactic use of AT in an attempt to decrease post-CPB bleeding is not recommended and should be avoided.[19,25] Fresh-frozen plasma (FFP) may be an alternative source for AT. Nonetheless, when available, the use of AT is preferred to FFP for treatment of heparin resistance, given the risks associated with FFP transfusion.

Minimizing Hemodilution

Hemodilution is a major risk factor for perioperative anemia and perioperative transfusions. All the guidelines strongly recommend implementing strategies to minimize hemodilution during cardiac surgery. These strategies may include the use of miniaturized CPB circuits (mini-circuits) with decreased priming volume, retrograde autologous priming of the CPB circuit, and modified hemofiltration.[19,25,26,45]

Mini-circuits have a smaller priming volume as well as reduced artificial extracorporeal surface due to elimination of the venous reservoir. In addition, the systems are completely closed to avoid blood–air contact. The reduced priming volume of mini-circuits offers potential benefits in reducing hemodilution. The smaller blood–air interface contributes to an attenuated inflammatory response to CPB.[63–66] Several meta-analyses have shown that the use of mini-circuits is associated with reduced postoperative bleeding and transfusion requirements as well as improved postoperative outcomes.[67,68] The clinical significance of the attenuated inflammatory response, however, still remains unclear and requires further investigation.

Retrograde autologous priming refers to priming of the CPB circuit using the patient's blood. This technique is a safe and inexpensive way to attenuate hemodilution and has been associated with decreased post-CPB allogeneic transfusions.[69–71]

Removing excess fluid after CPB by modified ultrafiltration may hemoconcentrate the blood as well as remove inflammatory mediators. In an RCT of 573 patients, modified ultrafiltration was associated with reduced post-CPB transfusion requirements as well as reduced incidence of postoperative pulmonary and neurological complications.[72] A more recent meta-analysis that evaluated 10 RCTs with 1004 patients demonstrated that ultrafiltration was associated with significantly decreased post-CPB bleeding and transfusions.[73]

Acute normovolemic hemodilution (ANH) is also recommended as a blood conservation measure during CPB. With this technique, a volume of blood is removed from the patient and stored in the operating room, just before the beginning of surgery (or CPB). The removed volume is replaced by crystalloid or colloid to maintain normovolemia. The blood is then transfused back to the patient after CPB. This practice is effective in reducing postoperative bleeding and RBC transfusions; however, it comes at the cost of lower hematocrit values during surgery. In a propensity score–matched retrospective analysis, Zhou et al[74] reported that ANH was associated with decreased RBC transfusions and a decreased risk for postoperative pulmonary infections. In a recently published meta-analysis that included 2439 patients in 29 RCTs, ANH was associated with a reduced need for RBC transfusions and reduced postoperative bleeding.[75] It seems that to achieve maximal benefit of ANH, ≥800 mL of blood needs to be removed before surgery.[76] In summary, preventive measures to minimize hemodilution or reduce the need for allogeneic blood transfusion are recommended in patients undergoing cardiac surgery.

Coagulation Monitoring and Transfusion Algorithms

All the guidelines support creation of a multidisciplinary patient blood management team and the design of transfusion algorithms based on predefined transfusion triggers measured by POC or other rapid-turnaround coagulation tests.[19–22,25]

The use of viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) has been the focus of extensive research in the management of bleeding after cardiovascular surgery. Multiple observational studies, randomized trials, and meta-analyses have demonstrated the efficacy of viscoelastic POC testing in reducing transfusion requirements and improving patient outcomes.[37–41,77–81] Published transfusion guidelines[19,21,22,25] also support this practice. Thus, it is the working group's opinion that viscoelastic coagulation tests are superior to conventional coagulation laboratory studies in guiding transfusion therapy in patients undergoing cardiovascular surgical procedures. Nonetheless, we recognize that these devices are still not widely available in many medical centers. Therefore, the use of conventional coagulation laboratory tests is recommended when viscoelastic tests are unavailable. In addition, it is important to mention that the cutoff values recommended in the viscoelastic algorithm (Figure 2) are for known devices that use the "cup and pin" technology. Newer devices that utilize different measurement platforms may have different threshold values and are yet to be extensively studied. Nevertheless, validation of the accuracy of the TEG 6S system (Haemonetics Corporation, Braintree, MA) in comparison with TEG 5000 has recently been reported.[82]

PLT Function Testing

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor has become the main antithrombotic treatment in patients presenting with cardiovascular pathological conditions such as acute coronary syndrome or myocardial infarction. While aspirin therapy alone is not associated with increased postoperative bleeding,[83] patients receiving DAPT are at increased risk for perioperative bleeding after cardiac surgery[84–87]; hence, many institutions have incorporated POC PLT function testing into the preoperative assessment of these patients, in an attempt to optimize the timing of surgery.[88–90] The working group suggests that POC PLT function testing be considered before surgery, if available, in patients treated with $P2Y_{12}$ inhibitors in whom there is a concern about the presence of active drug effect, and that surgery delayed, when possible, until the drug effects have disappeared.[25]

RBC Transfusion and Use of Cell Salvage

RBC transfusion may be required to maintain oxygen delivery and hemodynamic stability in the presence of active ongoing bleeding or severe anemia. All guidelines recommend the use of a restrictive blood transfusion strategy, maintaining Hb levels in the range 7–8 g/dL, because this was found to maintain adequate oxygen delivery while avoiding unnecessary allogeneic RBC transfusions. The most recent guidelines published by the European Association of Cardio-Thoracic Surgery and the European Association of Cardio-Thoracic Anaesthesiology do not define a specific Hb trigger for RBC transfusion, but rather recommend that transfusion decisions be made based on the patient's clinical condition.[25] However, a large RCT comparing restrictive with liberal RBC transfusion strategies in high-risk cardiac surgery patients, the TRICS III trial, as well as a recent consensus statement by an international panel of experts,[36,91,92] supports transfusion at an Hb level ≤7.5 g/dL. The members of the working group agree that an RBC transfusion threshold of Hb ≤7.5 g/dL is clinically reasonable and practical in most cardiac surgery patients and will be accepted by most practitioners.

Transfusion of cell-salvaged blood is strongly recommended and is associated with reduced perioperative anemia and decreased need for allogeneic RBC transfusions.[19–22,25,26] When compared with transfusion of blood from the cardiotomy suction, cell salvage was associated with less bleeding and reduced inflammation.[93] Recent studies have confirmed that the use of cell salvage was associated with decreased need for allogeneic transfusions,[94,95] as well as lower risk of postoperative pulmonary complications.[96]

Plasma/Prothrombin Complex Concentrate

FFP refers to plasma frozen within 8 hours after phlebotomy. Other plasma-derived products such as PF24 (plasma frozen within 24 hours after phlebotomy) and thawed plasma (FFP that is stored up to 5 days at a temperature of 1°–6°C after thawing) are also available in many countries

throughout the world. In clinical practice and even in the literature, it is a common practice to use these terms interchangeably. Therefore, throughout this document, the term FFP will refer to the use of any of these plasma products.

FFP may be effective in treating post-CPB coagulopathic bleeding with laboratory evidence of coagulation factor deficiency. Prophylactic administration of FFP during cardiac surgery, without evidence of coagulation factor deficiency, is not effective in reducing post-CPB bleeding and is not recommended.[97–99]

In patients requiring urgent operations, reversal of vitamin K antagonists was more effective with prothrombin complex concentrates (PCCs) compared to FFP, mainly due to a more rapid hemostatic effect.[100] Several studies[101–104] have reported that administration of PCC is also more effective than FFP in CPB-related coagulopathic bleeding and leads to decreased postoperative bleeding and transfusion. However, concerns regarding increased risk for postoperative acute kidney injury have been raised in 1 study.[102] Additional benefits of PCC over FFP include a significantly smaller administered volume and the avoidance of risks associated with plasma transfusion.

PCC is available in 3-factor and 4-factor preparations (4-factor PCC contains factor VII, whereas 3-factor PCC does not). In addition, some PCC preparations contain various amounts of heparin or other anticoagulants to avoid excessive coagulation.[105,106] Furthermore, due to high risk of increased thrombosis, administration of recombinant factor VIIa after the use of 4-factor PCC is not recommended. Recommendations for dosing of PCC are not completely established, because the use of PCC to treat post-CPB bleeding is regarded off-label. However, most centers use 10–15 u/kg to treat post-CPB bleeding and higher doses of 20–25 u/kg (and up to 50 u/kg in extreme cases) to reverse the effects of vitamin K antagonists. High-dose PCC may also be effective in reversing the effects of dabigatran and factor Xa inhibitors; however, with the recent development of specific reversal agents (idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors), the clinical use of PCC for reversal of these agents is anticipated to decrease.

In summary, both FFP and PCC may be used to reverse the anticoagulation effects of vitamin K antagonists and to treat post-CPB bleeding due to coagulation factors deficiency. Nevertheless, PCC (when available) offers several benefits over FFP and may be preferred especially when large volume of FFP is required to achieve hemostasis.

PLT Transfusion and Use of 1-Deamino-8-D-Arginine Vasopressin

Transfusion of PLTs is indicated in bleeding patients with thrombocytopenia or evidence of PLT dysfunction.[23,107] Recent guidelines recommend a trigger of ≤50,000/μL for PLT transfusion[21,23,25]; however, in the context of post-CPB bleeding, the PLT may be dysfunctional, and, thus, transfusion may be necessary even with a higher PLT count.[19,22,26] Therefore, the members of the working group agreed that in post-CPB bleeding, PLT should be transfused when the PLT count is ≤50,000/μL; however, in cases of severe ongoing bleeding and/or if evidence of PLT dysfunction exists, a higher threshold of 100,000/μL may be used. Evidence of PLT dysfunction may be demonstrated by PLT function assays or can be assumed if uremia exists if antiplatelet medications were recently administered.

1-Deamino-8-D-arginine vasopressin (DDAVP) improves PLT function by promoting the release of von Willebrand factor from endothelial cells. Desmopressin may be considered when PLT dysfunction exists or when acquired von Willebrand factor deficiency is suspected. However, the supporting evidence does not demonstrate a robust effect on bleeding or transfusion requirements.[108–111] Furthermore, routine prophylactic use of desmopressin without evidence of PLT dysfunction is not recommended.[19]

Fibrinogen Supplementation

Low levels of fibrinogen identified in the preoperative or the post-CPB period have been associated with increased bleeding and transfusion requirements.[112,113] Fibrinogen supplementation is recommended in post-CPB bleeding when there is evidence of hypofibrinogenemia (levels <150 mg/dL). Fibrinogen supplementation may be provided as cryoprecipitate or as human fibrinogen concentrate. Cryoprecipitate is not available in most European countries (due to safety concerns). In contrast, fibrinogen concentrate use in cardiac surgical patients is considered off-label in the United States and, therefore, not available in many centers. Studies evaluating post-CPB fibrinogen supplementation in cardiac surgery patients have yielded conflicting results. Two RCTs in patients undergoing complex cardiac surgery demonstrated decreased blood loss and transfusion of allogeneic blood products.[114,115] However, 2 other recent RCTs evaluating the use of fibrinogen concentrate in post-CPB bleeding did not confirm these results.[116,117] In fact, in the Randomized Evaluation of Fibrinogen versus Placebo in Complex Cardiovascular Surgery (REPLACE) trial, patients treated with fibrinogen concentrate had a significantly higher transfusion rate compared to placebo.[117] It is important to mention, however, that patients were enrolled into the study even if they did not exhibit post-CPB hypofibrinogenemia. In a recently published meta-analysis of 8 RCTs with 597 patients, administration of fibrinogen concentrate was associated with significantly decreased post-CPB blood loss compared to placebo, but there was no difference in mortality or other postoperative morbidities.[118]

In summary, prophylactic fibrinogen administration is not recommended for reducing postoperative bleeding and transfusion risks. However, in patients with a low fibrinogen level (<150 mg/dL) and persistent post-CPB bleeding, fibrinogen supplementation, provided as cryoprecipitate of fibrinogen concentrate, should be considered to reduce bleeding and blood transfusion.

Antifibrinolytic Agents

Antifibrinolytic medications are commonly used during cardiovascular surgical procedures with CPB to reduce post-CPB bleeding and allogeneic blood transfusions. The 2 most commonly used antifibrinolytic medications are the lysine analogs tranexamic acid (TXA) and ε-aminocaproic acid (EACA). A third product, aprotinin, was withdrawn from the market in 2007 due to safety concerns.[48,119] Since then the drug has been reapproved for use in several European

countries and in Canada, but still remains unavailable in the United States. Numerous studies have demonstrated the efficacy of antifibrinolytics in reducing bleeding and transfusion requirements after CPB.[120,121] However, many of these trials included low-risk patients with relatively short CPB times. The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial[50] compared TXA with placebo in patients undergoing coronary bypass surgery and demonstrated that patients who were randomly assigned to TXA therapy had a significantly reduced risk for reoperations due to postoperative bleeding, as well as a decreased need for transfusion of any blood products. Based on these data, all the transfusion guidelines support the use of antifibrinolytic agents in patients undergoing cardiac surgery with CPB.[19–22,25,26,45]

Recombinant Activated Factor VII

Off-label administration of recombinant factor VIIa (rFVIIa) is used for refractory severe post-CPB bleeding when other therapeutic options have failed. In a propensity score–matched analysis, Karkouti et al[122] demonstrated that the use of rFVIIa reduced blood loss and transfusion requirements after CPB in patients with severe intractable bleeding. A larger retrospective observational trial involving 18 cardiac surgery centers in Canada reported similar results.[123] A 3-arm placebo-controlled randomized trial[124] showed that there were significantly fewer reoperations for bleeding and fewer blood transfusions in patients receiving rFVIIa. There were also no significant differences in serious adverse events among groups; however, if a difference were to exist, the study was likely underpowered to detect differences in adverse events. Taken together, the off-label use of rFVIIa is effective in decreasing blood loss and allogeneic blood transfusions in patients with severe intractable post-CPB coagulopathic bleeding. The working group cautions that there may be a risk of arterial thrombosis with the use of rFVIIa that can result in myocardial infarction, especially in older patients[125]; therefore, when possible, clinicians should consider a lower dose of factor rFVIIa (20–40 μg/kg) to minimize the risk for thrombotic complications.

CONCLUSIONS/FINAL STATEMENT

Coagulopathy associated with cardiac surgery and CPB is complex and leads to allogeneic blood transfusions that are associated with a high rate of postoperative complications and mortality. Despite the existence of guidelines and consensus statements regarding perioperative blood management in cardiac surgery patients, practitioner adherence to these guidelines is low and significant variability in practices exists. Current guidelines are lengthy documents and may cause confusion if conflicting recommendations exist. The current summary statement of the SCA Blood Conservation Working Group is an attempt to create a clear and succinct document containing recommendations for perioperative blood management for cardiac surgical patients. Individualized therapy using POC-guided algorithms is recommended because they have been associated with improved patient outcomes when compared to standard laboratory-based or empiric transfusion therapy. The publication of these viscoelastic and nonviscoelastic testing algorithms will hopefully consolidate the existing evidence and provide clinicians with a simple tool that will aid them in managing the bleeding cardiovascular surgery patient. ■

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"And therefore never send to know to whom the bell tolls; it tolls for thee."

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