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EXPERT CONSENSUS DOCUMENT

Cardiac Surgical Bleeding, Transfusion, and Quality Metrics: Joint Consensus Statement by the Enhanced Recovery After Surgery Cardiac Society and Society for the Advancement of Patient Blood Management

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ABSTRACT

BACKGROUND Excessive perioperative bleeding is associated with major complications in cardiac surgery, resulting in increased morbidity, mortality, and cost.

METHODS An international expert panel was convened to develop consensus statements on the control of bleeding and management of transfusion and to suggest key quality metrics for cardiac surgical bleeding. The panel reviewed relevant literature from the previous 10 years and used a modified RAND Delphi methodology to achieve consensus.

RESULTS The panel developed 30 consensus statements in 8 categories, including prioritizing control of bleeding, prechest closure checklists, and the need for additional quality indicators beyond reexploration rate, such as time to reexploration. Consensus was also reached on the need for a universal definition of excessive bleeding, the use of antifibrinolytics, optimal cessation of antithrombotic agents, and preoperative risk scoring based on patient and procedural factors to identify those at greatest risk of excessive bleeding. Furthermore, an objective bleeding scale is needed based on the volume and rapidity of blood loss accompanied by viscoelastic management algorithms and standardized, patient-centered blood management strategies reflecting an interdisciplinary approach to quality improvement.

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CONCLUSIONS Prioritizing the timely control and management of bleeding is essential to improving patient outcomes in cardiac surgery. To this end, a cardiac surgical bleeding quality metric that is more comprehensive than reexploration rate alone is needed. Similarly, interdisciplinary quality initiatives that seek to implement enhanced quality indicators will likely lead to improved patient care and outcomes.

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EXECUTIVE SUMMARY AND KEY CONSENSUS STATEMENTS

Executive Summary

Although excessive perioperative bleeding in cardiac surgery is associated with significant adverse outcomes, current quality metrics for control of bleeding are insufficiently comprehensive. Key areas for improvement include the prioritization of bleeding control throughout the case, use of a surgical bleeding checklist prior to closure, and encouraging early reexploration when appropriate. Additional important process variables include optimal use of antifibrinolytics, cessation of antiplatelets, and appropriate patient blood management strategies to reduce the need for transfusions. Other critical considerations are preoperative risk scoring based on potentially modifiable, nonmodifiable, and procedural risk factors, and a universal definition and method of grading excessive bleeding. Finally, the development of new performance quality indicators beyond reexploration rate, such as the use of bleeding checklists and time to reexploration, are needed to improve patient outcomes.

Key Statements:

1. A universal definition of excessive bleeding is required for the early postoperative period.
2. Production pressure may be an unmeasured risk factor for bleeding in cardiac surgery.
3. Control of bleeding throughout the cardiac surgical procedure should be a high priority.
4. Prompt reexploration for bleeding reduces the risk of adverse outcomes.
5. Platelet function should be assessed prior to cardiac surgery in patients at risk of bleeding due to platelet dysfunction.
6. Viscoelastic testing can help to identify the underlying cause of bleeding and direct therapy in real time.
7. Red blood cell transfusion should not be used empirically unless bleeding is considered severe. Non-red blood cell transfusion should be guided by laboratory confirmation of significant coagulopathy.
8. Standardization is needed to reduce unwanted variability in transfusions, treatment algorithms, and reexploration rates for managing cardiac surgical bleeding.
9. Routine auditing and benchmarking of patient data regarding bleeding management will improve the quality of care.
10. Quality indicators for cardiac surgical bleeding should be expanded beyond reexploration rates to encompass factors such as surgical bleeding checklists and time to reexploration.
11. The risks of stopping anticoagulant and antiplatelet therapy must be individualized and balanced against the benefits of continuing therapy.
12. Prophylactic antifibrinolytic therapy reduces blood loss and transfusions in cardiac surgery and should be administered to cardiac surgical patients undergoing cardiopulmonary bypass, unless contraindicated.

INTRODUCTION

Excessive intraoperative and postoperative bleeding is a major complication associated with cardiac surgery, occurring in up to 15% of patients.[1-4] Previous studies have shown that excessive cardiac surgical bleeding is an independent risk factor for morbidity and mortality[5,6] and also incurs a significant economic burden.[7] Excessive bleeding is associated with higher rates of reexploration and blood component transfusions, both of which adversely affect patient outcomes.

One of the main quality indicators currently used to measure cardiac surgical bleeding is the reexploration rate; however, this does not fully

Abbreviations and Acronyms

AKI = acute kidney injury
ANH = acute normovolemic hemodilution
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CPB = cardiopulmonary bypass
DOAC = direct oral anticoagulant
EACA = ε-aminocaproic acid
E-CABG = European registry of Coronary Artery Bypass Grafting
ERAS = Enhanced Recovery After Surgery Cardiac Society
ICU = intensive care unit
LOS = length of stay
PBM = patient blood management
PCC = prothrombin complex concentrate
RBC = red blood cell
rFVIIa = recombinant factor VIIa
SABM = Society for the Advancement of Patient Blood Management
TXA = tranexamic acid
UDPB = Universal Definition for Perioperative Bleeding
VIBe = Validated Intraoperative Bleeding

capture the myriad processes and variables that may be responsible for, or influence, perioperative bleeding. Improving and expanding quality metrics used in cardiac surgery is therefore essential. Metrics that prioritize prevention, control, and timely resolution of bleeding could be considered key aspects of any future quality metrics. Moreover, methods of increasing provider awareness, education, and knowledge of hemostatic agents and practices are vital to improving patient clinical outcomes and enhancing resource efficiency.[8] To this end, an expert panel was convened by the Society for the Advancement of Patient Blood Management (SABM) and the Enhanced Recovery After Surgery Cardiac Society (ERAS Cardiac). The panel reviewed the current literature on cardiac surgical bleeding using a modified RAND Delphi methodology, with the aim of developing clinical consensus statements focusing on the reporting and control of cardiac surgical bleeding.

METHODS

EXPERT PANEL. An interdisciplinary panel of 13 experts in cardiac surgery and patient blood management (PBM) was convened. The panel members were selected based on their academic qualifications, subject matter expertise, and relevant clinical experience. All panel members reviewed the literature search results, established consensus statements for controlling cardiac surgical bleeding, and drafted and critically reviewed the manuscript. In addition, 3 secondary panel members drafted and critically reviewed the manuscript.

LITERATURE SEARCH. Initial literature searches were performed in July 2023 using PubMed and Web of Science (Web of Science Core Collection and BIOSIS databases), yielding 3861 unique publications for screening (see the Supplemental Material for full search terms). The searches were filtered for articles published in English in the last 10 years (from 2013 onward). In addition to the primary searches, separate searches in PubMed and Web of Science were performed to identify publications related to quality initiatives in cardiac surgery. These searches produced a further 65 and 39 publications for screening, respectively. The panel also provided any additional relevant literature that had not already been identified by the literature search.

The literature search results were screened according to the following inclusion criteria: randomized clinical trials and prospective and retrospective observational clinical trials in human adult patients undergoing cardiac and/or aortic surgery up to and including the aortic arch. Systematic reviews and meta-analyses were also included, and standard reviews and surgical guidelines were considered for the quality indicator searches. Preclinical studies, case reports, study protocols, and congress materials were excluded, as were studies in animals, pediatric patients, or those detailing vascular surgery. An overview of the literature screening process is provided in the Supplemental Figure.

PANEL SURVEY AND ACHIEVEMENT OF CONSENSUS. Select panel members (S.O., R.S., and A.S.) developed initial consensus statements. A multiple-choice survey with a 5-point Likert scale was used to gauge consensus on the statements. All panel members completed the survey ahead of attending a face-to-face meeting in Washington, DC, United States, in September 2023.

The survey responses were discussed in the meeting, and the RAND Delphi (modified) process was used to establish consensus. Consensus was defined as a minimum agreement threshold of 75% of respondents agreeing (strongly agree/agree) or disagreeing (strongly disagree/disagree) with a survey statement. Statements meeting the threshold for consensus were discussed first, and adjustments were made to the statements, if necessary, for brevity and/or clarity of wording. Discussions then focused on statements that were close to meeting consensus and statements that had no consensus. Panel members were allowed to change their responses, and where required, statements were adjusted, combined, or removed.

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All changes were agreed upon by formal voting. Minor revisions to the consensus statements were made after the meeting and during manuscript development when deemed necessary by the panel.

CONSENSUS STATEMENTS

1. **Definition and Grading of Bleeding**
   - *A universal definition of excessive bleeding is required for the early postoperative period.*
   - *The perioperative team should seek to implement the routine use of an objective, validated bleeding scale to assess bleeding and guide management.*

The threshold demarcating excessive bleeding in cardiac surgery is not well defined, and this is further hampered by many studies not reporting absolute volumes of blood loss. Previously suggested thresholds include the Universal Definition for Perioperative Bleeding (UDPB) level of >1000 mL within 12 hours indicating severe bleeding[9] and the Bleeding Academic Research Consortium definition of ≥2000 mL chest tube output within 24 hours of coronary artery bypass grafting (CABG).[10] Other definitions used in clinical trials include active bleeding, defined as blood loss >1.5 mL/kg/h for 6 consecutive hours within the first 24 hours,[11] or major bleeding classified as blood loss >900 mL in the first 12 hours.[12] However, because these definitions vary in the variables measured and the thresholds used, what constitutes excessive bleeding is potentially confusing, leading to subsequent unnecessary delays in treatment.

As such, a standardized, universally adopted definition of excessive bleeding is required to eliminate any doubt about when to take action.

Furthermore, clear guidance is needed on how to properly quantify intraoperative blood loss. Assessment scales that measure the amount of perioperative bleeding can be valuable tools for guiding treatment. Previous studies have shown generally positive results when using bleeding scales, such as the European registry of Coronary Artery Bypass Grafting (E-CABG) grading score, the UDPB, and the Bleeding Academic Research Consortium bleeding definition, to assess severity and prognostic implications of intraoperative bleeding.[9,13,14] Another commonly used bleeding scale is the World Health Organization bleeding scale.[15]

However, grading scales such as these have several limitations: most notably, scales such as the E-CABG and UDPB are not entirely based on the direct measurement of intraoperative or postoperative blood loss, but use blood component utilization to quantify bleeding.[9,13] Also an issue is subjectivity in the grading of bleeding, which is particularly evident with the widely used World Health Organization scale.[15] Therefore, there is a need for a validated bleeding scale based solely on quantitative measures such as volume and rate of bleeding.

Bleeding scales such as the SPOT GRADE and Validated Intraoperative Bleeding (VIBe) scales[16,17] offer more objective measurements of bleeding assessment. In particular, the VIBe scale has been validated in various other surgical specialties,[18-20] with a modeling study concluding that its use would likely improve surgical efficiency, reduce intraoperative bleeding, and reduce costs associated with the transfusion of blood components.[21] However, the SPOT GRADE and VIBe bleeding scales are limited to intraoperative bleeding assessment,[16,17] and additional objective bleeding scales would be required to assess postoperative bleeding. A comparison of the various bleeding scales discussed is provided in Table 1.[9,10,15-17,22-25]

2. **Predictors of Bleeding**
   - *There are potentially modifiable and nonmodifiable risk factors that increase the likelihood of excessive perioperative bleeding.*
   - *There are patient and procedural factors that predict perioperative bleeding in cardiac surgery.*
   - *The use of a preoperative risk score assists in predicting bleeding.*
   - *A dynamic risk assessment process can facilitate targeted bleeding control.*
   - *Production pressure may be an unmeasured risk factor for bleeding in cardiac surgery.*

Various preexisting factors can influence the risk of a patient experiencing excessive bleeding related to cardiac surgery (Table 2).[26-33] Factors that are potentially modifiable, such as the cessation of anticoagulant/antithrombotic medications before surgery, should be addressed to reduce the risk of excessive bleeding. Another modifiable risk factor for receiving red blood cell (RBC) transfusion is the presence of preoperative anemia and iron deficiency.[34] However, it is also important to note nonmodifiable factors, such as age, race/ethnicity, and sex, and acknowledge that these may make excessive bleeding more likely.[26,35-37] In addition, there are several procedural factors that potentially increase the risk of bleeding that should also be considered.

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TABLE 1 Characteristics of Common Bleeding Scales Used in Cardiac Surgery

Bleeding Scale	Main Components	Advantages	Disadvantages
E-CABG[22]	· Amount of blood components transfused · Need for reexploration for excessive bleeding	– Relatively simple definition of bleeding – Accounts for postoperative bleeding – Incorporates an additive score	– Based on surrogate outcomes of bleeding
UDPB[9]	· Delay in sternal closure · Postoperative chest tube blood loss within 12 hours · Amount of blood components transfused · Prothrombotic drugs administered · Need for reexploration or tamponade	– Widely used – Incorporates measurement of blood loss volume	– Complex grading system – Partially based on surrogate outcomes of bleeding
BARC[10]	· Overt signs of bleeding · Hemoglobin level · Need for reexploration or tamponade · Requirement for IV vasoactive agents · Intracranial hemorrhage · Transfusion of whole blood or pRBCs within 48 hours · Chest tube output within a 24-hour period	– Combines both laboratory and clinical assessments – Specifically includes assessment of CABG-related bleeding – Validated in acute coronary syndrome[23] – Incorporates measurement of blood loss volume	– Minor grades potentially not clinically relevant – Complex grading system – Partially based on surrogate outcomes of bleeding – Designed based on consensus
WHO[15]	· Visual assessment of hemorrhage	– Widely used – Relatively simple definition of bleeding – Does not require laboratory assessment	– Subjective – Associated with high interobserver variability[24] – Minor grades potentially not clinically relevant
SPOT GRADE[17]	· Visual assessment of hemorrhage · Expected interventions · Rate of blood flow	– Clinically validated[25] – Meets US FDA requirements for use in determining the degree of bleeding in a surgical wound – Based on quantitative determination of blood flow	– Some subjective elements – Limited to intraoperative assessment
VIBe[16]	· Visual presentation · Anatomic appearance · Estimated rate of blood loss	– Designed based on US FDA criteria for clinician-reported scales – Validated in multiple surgical disciplines – Includes an assessment of blood loss	– Some subjective elements – Limited to intraoperative assessment

BARC, Bleeding Academic Research Consortium; E-CABG, European registry of Coronary Artery Bypass Grafting; IV, intravenous; pRBCs, packed red blood cells; UDPB, Universal Definition of Perioperative Bleeding; US FDA, United States Food and Drug Administration; VIBe; Validated Intraoperative Bleeding; WHO, World Health Organization.

Many of these risk factors are incorporated into bleeding control protocols and preoperative risk scores that can assist in the prediction of excessive bleeding. For example, Karkouti and colleagues[26] developed a prediction rule and risk score accurately identifying patients based on their risk for excessive bleeding and subsequent massive blood transfusion. Risk scores such as Papworth, WILL-BLEED, and HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly) are other prediction tools that can be useful in identifying at-risk patients. In a retrospective analysis of the E-CABG registry in 3744 patients with an additive score for prediction of severe bleeding (E-CABG grades 2-3), the WILL-BLEED score was significantly associated with increased bleeding risk.[38] In another retrospective analysis of 550 CABG patients, the WILL-BLEED and Papworth scores were both correlated with the subsequent presence of severe bleeding.[39]

In addition to assessing preoperative risks, ongoing bleeding risk assessment, such as measurement and correction of platelet, fibrinogen, and coagulation indices,[40] is needed, because bleeding related to cardiac surgery is a dynamic process affected by multiple factors.

Aside from patient and procedural factors, an often-silent influence on medical practice is "production pressure," for which no existing risk prediction model exists. This concept reflects overt or covert pressures and incentives on personnel to have production be their primary priority.[41] In health care, production pressure can contribute to medical errors and poor patient outcomes[42,43] and can result from several factors related to the structure of health care systems and organizations.[44] Factors such as time pressures, high workloads, underresourcing, and revenue targets can all contribute to production pressures and negatively impact both staff and patients.[44] In cardiac surgery, such factors may result in medical errors, superficial investigation

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TABLE 2 Potentially Modifiable and Nonmodifiable Risk Factors and Patient and Procedural Factors That Can Predict Perioperative Bleeding in Cardiac Surgery[a]

Patient Factors		
Potentially Modifiable	**Nonmodifiable**	**Procedural Factors**
Preoperative anticoagulant, antiplatelet, or antithrombotic medications	Age	Type and complexity of procedure
Preoperative anemia/hemoglobin level	Race/ethnicity	Urgency of procedure/surgical priority
Platelet count	Sex	Temperature management
Fibrinogen level	Genetic factors related to coagulopathy	Use of cell recovery methods
Body mass index	Cardiac function before surgery	Cardiopulmonary bypass duration
Malnutrition	Frailty	Skill of surgeon performing procedure
Comorbidities, eg, hypertension and diabetes		Use of bleeding checklists Improper heparin reversal

[a]Data were derived from.[26–33]

for bleeding before chest closure, or hesitancy/delay in reexploration of actively bleeding patients. Reducing production pressure requires resourcing and analysis of workflows to manage the unpredictable nature of health care workloads effectively. This leads to implementing policies and procedures that augment the safety culture.[42,44]

3. **Patient Outcomes Related to Excessive Perioperative Bleeding and Reexploration**
   - *Control of bleeding throughout the cardiac surgical procedure should be a high priority.*
   - *Excessive perioperative bleeding in cardiac surgery is associated with an increased risk of adverse outcomes.*
   - *Excessive intraoperative and postoperative bleeding in cardiac surgery significantly increases the likelihood of the need for reexploration.*
   - *Prompt reexploration for bleeding reduces the risk of adverse outcomes.*

Excessive bleeding in cardiac surgery is associated with an increased risk of postoperative complications, even for low-risk patients.[27,45] Adverse outcomes associated with excessive bleeding include stroke, acute kidney injury (AKI),[4,45] prolonged ventilation, longer hospital and intensive care unit (ICU) lengths of stay (LOS), and increased 30-day mortality.[1,6,12,27] Furthermore, excessive bleeding is associated with increased transfusion of blood components, which in itself is associated with an increased risk of morbidity and 30-day mortality.[28] Several studies have shown that patients experiencing excessive bleeding of any etiology during and after cardiac surgery are more likely to undergo reexploration.[29,30,46]

Reexploration has been associated with various adverse outcomes, including stroke, sepsis, cardiac arrest, prolonged ventilation, longer ICU and hospital LOS, AKI, and higher mortality rates.[31,47,48] Reexploration for bleeding has also been associated with failure to rescue; that is, death that occurs after the development of a complication, such as bleeding, that was potentially treatable.[49]

The decision to reexplore should be based on defined clinical criteria; however, considerable variability exists in the thresholds used. The traditional Kirklin/Barratt-Boyes criteria have defined the need for reexploration as bleeding of >500 mL during the first hour post-surgery, >400 mL during each of the first 2 hours, >300 mL in each of the first 3 hours, or >1000 mL or >1200 mL in total during the first 4 or 5 hours post-surgery, respectively.[46] Excessive bleeding that restarts and sudden massive bleeding are also indications that reexploration is needed.[46,50] Other studies have used slightly different blood loss volumes and/or other objective criteria, such as signs of tamponade or surgical bleeding, hemodynamic status, and laboratory indicators, with the decision ultimately made based on the perioperative team's clinical judgment.[30,31,51]

Reexploration for bleeding, when required, is best performed early, before hemodynamic compromise or signs of end-organ malperfusion. Early reexploration is preferable to over-zealous ("time-buying") treatment with allogeneic blood components and pharmacologic agents.[52] A Canadian retrospective study found that 358 patients who underwent delayed reexploration had a 3-fold greater risk of perioperative mortality than 303 patients reexplored on the day of

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surgery (odds ratio, 6.4 [95% CI, 4.7-8.9] vs 2.0 [95% CI, 41.3-3.1], respectively; $P < .001$).[52] Moreover, a retrospective single-center study reporting 0% mortality in patients (n = 75) undergoing reexploration for excessive bleeding after open cardiac surgery attributed the absence of mortality to early surgical reexploration of bleeding patients. Time to reexploration after moving to ICU was <10 hours in all patients (<5 hours in 49 patients [65.3%] and <10 hours in 26 [34.7%]).[46] In another retrospective cohort study (n = 139), reexploration for bleeding that was delayed for ≥5 hours was associated with an increase in stroke and AKI ($P = .03$). The expert panel also noted that prompt reexploration may be particularly pertinent for noncoagulopathic bleeding etiologies, where surgical intervention may be required to remedy an anatomic source of bleeding.

Because transfusions and delayed reexploration are associated with significantly increased morbidity and mortality,[53] prompt control of anatomic, noncoagulopathic, and surgical bleeding should be a high priority.

4. **Management of Coagulopathy and Viscoelastic Testing**
   - *Viscoelastic testing algorithms can reduce bleeding, reexploration, and blood component transfusion in cardiac surgery.*
   - *Platelet function should be assessed prior to cardiac surgery in patients at risk of bleeding due to platelet dysfunction.*
   - *Viscoelastic testing can help to identify the underlying cause of bleeding and direct therapy in real-time.*

Viscoelastic testing is a useful tool for promptly identifying clinically relevant coagulation defects throughout the intraoperative and early postoperative phases of care. Although routine preoperative viscoelastic testing has not been shown to predict bleeding in the entire cardiac surgery population,[54] it can help identify those at increased bleeding risk due to an underlying coagulopathic state. In patients with active bleeding, the etiology of the coagulopathy can be rapidly identified, allowing precise therapeutic management.

Several studies have shown the capability of intraoperative point-of-care viscoelastic testing[55-57] to help determine the etiology of coagulopathy more quickly than with standard laboratory tests. In an analysis of 65 patients who underwent cardiac surgery with cardiopulmonary bypass (CPB), clotting variables measured by viscoelastic testing, such as clotting time, maximal clot firmness, and α-angle, were significant predictors of increased postoperative bleeding.[55] In another analysis of 89 patients undergoing combined cardiac surgical procedures, clot strength measured using viscoelastic testing had similar sensitivity for 24-hour blood loss and greater sensitivity for 6-hour blood loss compared with plasma-based fibrinogen concentrations.[58] Aside from the specific results provided by viscoelastic tests, a normal viscoelastic profile in the setting of ongoing bleeding can inform practitioners of the increased likelihood of a surgical source of bleeding.

Using management algorithms guided by viscoelastic testing has been associated with reduced perioperative bleeding. A retrospective 10-year study of hemorrhage-reducing interventions in almost 20,000 cardiac surgery patients found that a viscoelastic testing-guided diagnostic and therapeutic approach resulted in a significant ($P = .006$) reduction in postoperative bleeding.[59] Viscoelastic testing has also been associated with reductions in transfusions of RBCs, non-RBC components, rates of reexploration, hospital LOS, and related costs.[60-64]

In a United States retrospective analysis of 677 cardiac surgery patients, viscoelastic testing-guided transfusion management during and immediately after cardiothoracic surgery resulted in significantly reduced postoperative LOS (9.9 vs 11.3 days, $P = .04$), the incidence of reexploration (3.5% vs 7.1%, $P = .04$), and an ~3-fold decrease in 6-month mortality (odds ratio, 2.98; 95% CI, 1.13-7.85). The mean number of units of packed RBCs and plasma were also significantly reduced in the perioperative period.[65]

Platelet function testing can be helpful in identifying patients at risk of bleeding related to platelet defects. However, the lack of normal values in different patient populations and the various testing instruments make these tests difficult to standardize.[66] Certain point-of-care tests may have limitations at the extremes of hemodilution seen on CPB, although most function well in the broad range of values seen in cardiac surgery patients. Platelet function testing is particularly effective in the preoperative interval for patients on antiplatelet therapies such as $P2Y_{12}$ inhibitors and glycoprotein IIb/IIIa inhibitors, where there is sufficient time to evaluate test results.[67-69] Platelet function testing should guide timing for cardiac surgery and assess the degree of platelet inhibition in urgent cardiac surgery

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patients receiving $P2Y_{12}$ inhibitors.[59,70] Preoperative low platelet reactivity in patients taking $P2Y_{12}$ inhibitors is associated with increased bleeding and blood component transfusion.[71-75]

Management of coagulopathy using viscoelastic testing may guide clinical decision making, enable timely hemostatic interventions, and thus improve patient outcomes.[76,77] However, it is important to recognize that surgical and coagulopathic bleeding are not mutually exclusive. Therefore, it is vital to use clinical context in conjunction with multiple coagulation tests to interpret the etiology of the bleeding.[58]

5. **Patient Blood Management**
   - *RBC transfusion should not be used empirically unless bleeding is considered severe. Non-RBC transfusion should be guided by laboratory confirmation of significant coagulopathy.*
   - *An evidence-based hemoglobin threshold and defined clinical criteria should be met before nonemergent RBC transfusion.*
   - *Standardization is needed to reduce unwanted variability in transfusions, treatment algorithms, and reexploration rates for managing cardiac surgical bleeding.*
   - *Intraoperative RBC recovery reduces allogeneic RBC transfusion.*
   - *Acute normovolemic hemodilution can effectively reduce allogeneic RBC transfusion; however, the degree of hemodilution should be monitored, because it may lead to coagulopathy.*
   - *Retrograde autologous priming is an effective method to limit hemodilution and reduce RBC transfusion.*

Blood transfusion should not be the default treatment option in bleeding patients due to the known associated morbidity.[78,79] Except in cases of massive bleeding, defined clinical criteria should be used to confirm the degree of bleeding and related anemia before transfusion, and a conservative approach to transfusion may still be preferable. A large, multicenter, noninferiority trial (Transfusion Requirements in Cardiac Surgery [TRICS] III) showed that a restrictive RBC transfusion strategy (hemoglobin threshold of <7.5 g/dL) in moderate- to high-risk patients undergoing cardiac surgery resulted in fewer units of RBCs transfused and was noninferior to a liberal transfusion strategy (hemoglobin threshold of <9.5 g/dL in the operating room or ICU and <8.5 g/dL on the non-ICU ward) with regards to major morbidity and death.[80]

The recent Cost-effectiveness and Cost-utility of Liberal vs Restrictive Red Blood Cell Transfusion Strategies in Patients With Acute Myocardial Infarction and Anaemia (REALITY) and Myocardial Ischemia and Transfusion (MINT) trials have also demonstrated that a liberal transfusion strategy does not reduce the risk of myocardial infarction or death within 30 days[81-83]; thus, a restrictive strategy affording exposure to fewer blood components may be beneficial. The perioperative team should be educated to encourage consideration of both hemoglobin concentration and defined clinical criteria, which are important to avoid unnecessary transfusions. PBM also affirms that blood component therapy should be tailored to the individual patient's acquired or inherited coagulopathy.[82]

The implementation of structured PBM strategies can result in a significant reduction in the number of blood component transfusions and associated complications.[84-87] A goal-directed PBM initiative in cardiac surgery at a United States hospital—which included preoperative and postoperative anemia management, greater emphasis on autologous cell recovery and surgical bleeding control, and a restrictive transfusion threshold—resulted in a significant reduction in transfusion of blood components, AKI, LOS, and costs.[88] Similar positive outcomes were seen in an Australian hospital that implemented a bleeding control algorithm centered on point-of-care coagulation testing, with reductions in the use of allogeneic blood components, reexploration rates, and LOS.[89]

PBM practices, however, can vary widely among surgeons and surgical centers,[90,91] and there appears to be a need for standardized, patient-centered, evidence-based protocols to improve outcomes. Successful PBM strategies require health care professionals to agree on best practices as part of an interdisciplinary team approach to bleeding. Education and collaboration are necessary aspects of this standardization.[90] Nonetheless, despite numerous examples of successful PBM strategies existing in the literature, additional studies are still needed to enhance the evidence base to support their use and guide clinical teams in their implementation.

Individual strategies to reduce bleeding and improve outcomes in cardiac surgery include intraoperative red cell recovery regimens and acute normovolemic hemodilution (ANH). Intraoperative red cell recovery regimens have been shown to significantly reduce the subsequent need for allogeneic blood transfusions and

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improve patient outcomes.[92-94] However, a small increased risk of perioperative residual heparin should be noted, and the exclusion of other procoagulation components may potentially result in blood coagulation impairment.[95-97] Large-volume ANH has been shown to significantly reduce postoperative bleeding and both RBC and non-RBC component use in cardiac surgery patients without an increase in major adverse outcomes or mortality.[98-101] However, the evidence base is relatively small, with most studies not powered to assess safety, and the hemodilution procedures vary among studies. There is also a need for ANH to be performed by teams who use this procedure as part of standard practice to avoid large-volume hemodilution. Care must be taken not to administer large volumes of colloids or crystalloids, which can increase the risk for coagulopathy.[100,102,103]

Retrograde autologous priming has also been shown to significantly reduce transfusion rates,[104,105] although no significant effect on bleeding, reexploration rates, or mortality has been observed.[104] The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of ExtraCorporeal Technology/SABM guidelines suggest a role for retrograde autologous priming in PBM, stating that "retrograde autologous priming of CPB circuits should be used wherever possible" (American College of Cardiology/American Heart Association Class I, Level B-R).[106]

6. **Quality Improvement**
   - *Routine auditing and benchmarking of patient data regarding bleeding management will improve the quality of care.*
   - *Multidisciplinary education, decision support, memory aids, checklists, routine data sharing, and feedback are important tools for improving quality.*
   - *Quality indicators for cardiac surgical bleeding should be expanded beyond reexploration rates to encompass factors such as surgical bleeding checklists and time to reexploration.*

Excessive bleeding is sometimes an unavoidable reality of cardiac surgery and is associated with adverse patient outcomes. Although various tools and strategies exist to attenuate the risk of bleeding and encourage best practices, routine auditing and benchmarking are key aspects of standardizing patient care and can identify opportunities to improve care.

Benchmarking involves reviewing the institutional performance of a specific quality indicator and comparing it with external acuity-adjusted rates and best practice models to improve the quality of care. For example, after transfusions were benchmarked as higher than expected in a United States cardiac surgical center, electronic medical record data were collected to create provider-specific audits and overall rankings, with subsequent feedback given to physicians. This, along with convening an interdisciplinary task force to develop a PBM strategy, proved effective in promoting quality improvement in blood component use.[107]

A summary of PBM best practice in cardiac surgery by the Society of Cardiovascular Anesthesiologists Blood Conservation Working Group found that all existing PBM guidelines supported the creation of a multidisciplinary PBM team.[108] A report of the successful implementation of a formal hemostasis checklist in a United States hospital showed the importance of forming multidisciplinary PBM teams, with this considered a key factor in obtaining buy-in from all involved. The report also underlined the value of education initiatives, because successful implementation was facilitated by an extensive educational in-service for all surgical residents, fellows, and support staff, with clear communication provided on the importance to patient care.[109]

Furthermore, the implementation of a bleeding control quality initiative in an Australian cardiac surgery unit highlighted the importance of support from multidisciplinary clinical leads, the availability of educational materials, and continuous evaluation to ensure that practice change is sustained. The development of a permanent blood management clinical nurse consultant role to facilitate continued education and monitoring was a particularly successful component of the initiative.[111]

The rate of reexploration is a useful indicator of quality in cardiac surgery. Still, more is needed to accurately assess the quality of measures taken to minimize cardiac surgical bleeding. Furthermore, using the reexploration rate alone can, in some cases, function as a punitive measure, penalizing those surgeons who choose to reexplore early and potentially discouraging or delaying reexploration even when clinically indicated.[53] The fact that reexploration rate is a component of The Society of Thoracic Surgeons Adult Cardiac Surgery Database star rating system can discourage surgeons from promptly reexploring patients.[110]

Another factor that may dissuade surgeons from performing reexploration for bleeding is the

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stigma of reoperation. Patients and families may more readily accept that a blood transfusion is an expected outcome after cardiac surgery compared with a reoperation. This issue could be partially mitigated by discussing the risk of bleeding preoperatively as part of informed consent, with reexploration clearly documented as a potential outcome for surgery should patients bleed in the postoperative setting. In addition, discussion with families regarding the benefits of decreased transfusions with a timely reoperation may also be useful.

Additional factors that could be used as quality indicators include time to reexploration, for which the benefits of prompt action have already been discussed, and the use of an intraoperative, preclosure surgical bleeding checklist. Routine use of surgical bleeding checklists has been shown to improve outcomes, including reducing rates of reexploration for bleeding and cardiac tamponade.[109,112,113] Crucial elements of these effective checklists include educational initiatives, ease of use, memory aids, and evaluation and feedback to facilitate implementation. Other considerations to note include the number of units of blood transfused, the volume of blood components administered, coagulation tests performed before reexploration, and an estimate of the volume of blood lost during cardiac surgery.

7. **The Use of Antithrombotic Agents**
   - *The risks of stopping anticoagulant and antiplatelet therapy must be individualized and balanced against the benefits of continuing therapy.*
   - *Prior to elective surgery, in the absence of coronary artery disease (CAD) or a strong antithrombotic indication, aspirin should be discontinued to reduce the risk of bleeding.*

Standardized recommendations exist for the discontinuation/reversal of direct oral anticoagulants (DOACs) and the optimal cessation time for antiplatelet therapy before cardiac surgery. However, balancing the risks of stopping therapy against the benefits of continuing therapy remains challenging. Therefore, treatment decisions must be individualized based on the patient's clinical status and predicted risk of bleeding.

In elective procedures, it is generally recommended to stop DOAC therapy 2 to 4 days before major surgery or longer if renal function is impaired.[114] The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) trial provided insight regarding the safety of discontinuing DOACs without bridging to heparin. For major surgery, holding DOACs for >5 half-lives (>48 hours with typically <5% DOAC residual activity) in patients with normal renal function was associated with a low risk of major bleeding or thromboembolism.[115] The decision to proceed in patients with renal failure is more challenging, and increasing the length of hold time to a longer interval was proposed in PAUSE. Although definitive evidence supporting measurement of anti-Xa activity in the case of apixaban and rivaroxaban exposure does not exist, assaying for anti-Xa activity before surgery may help, particularly when there is no evidence of residual effect.

A similar protocol can potentially be applied for urgent cardiac surgical procedures, provided it is considered safe to delay the surgery.[116] A more rapid approach is often needed in emergency surgery.[117] In this situation, prothrombin complex concentrate (PCC) administration has been shown to be effective and is often the recommended treatment for the reversal of anticoagulation in emergency cardiac surgery patients.[106] A direct antidote may also be considered, although these are often costly and may have adverse consequences in cardiac surgery.[118-120] Idarucizumab is a specific reversal agent for oral direct thrombin inhibitors and can be used.[120] Andexanet alfa is a specific antidote for particular oral factor Xa inhibitors; however, it can be associated with subsequent heparin resistance after administration, which makes this drug a less desirable strategy in cardiac surgical patients.[119,121] Another option under investigation for patients undergoing emergency cardiac surgery on DOAC or ticagrelor therapy is intraoperative hemoadsorption. Further studies are required to confirm its clinical effectiveness in decreasing perioperative bleeding and bleeding-related complications, as well as its overall safety.[122-124]

For antiplatelet therapy, there is broad consensus on the optimal timing of preoperative cessation for the most common therapies: a standard of 3 days for ticagrelor, 5 days for clopidogrel, and 7 days for prasugrel, with aspirin continued until surgery.[106,114] However, cessation of these therapies may not be possible in some patients, in which case preoperative assessment of antiplatelet drug activity and point-of-care platelet function testing can be used to assess the risk of bleeding and guide surgical decision making.[106,114]

It is well established that aspirin reduces myocardial infarction in patients with CAD and thrombotic risk in CABG patients.[125,126] In patients with CAD undergoing CABG, postoperative bleeding was less in patients who continued

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aspirin until the day before surgery compared with patients who received enoxaparin.[127] However, compared with no anticoagulant therapy, aspirin has been associated with an increased risk of bleeding and subsequent transfusion and reexploration. The risk-benefit analysis in these patients should consider the indication for aspirin. Discontinuation of aspirin for 7 days before surgery should be considered in the absence of CAD or a strong antithrombotic indication.[114] In patients with a potential indication for continuing aspirin, the preventative effects should be balanced against the risk of bleeding.[114,128]

8. Treatments for Cardiac Surgical Bleeding

- *Prophylactic antifibrinolytic therapy reduces blood loss and transfusions in cardiac surgery and should be administered to cardiac surgical patients undergoing CPB unless contraindicated.*
- *Owing to its thrombotic risk, recombinant factor VIIa (rFVIIa) should be used cautiously, and its use should be restricted to extreme circumstances of intractable bleeding.*
- *PCCs are effective at reducing transfusions in patients with documented coagulopathies as part of a comprehensive PBM program.*
- *Where possible, a 4-factor PCC should be used rather than rFVIIa alone.*
- *Fibrinogen supplementation can effectively decrease blood loss and blood component utilization in patients with acquired hypofibrinogenemia.*

Antifibrinolytics are a key therapeutic intervention for blood conservation in cardiac surgery,[129] and the most used of these are the lysine analogues tranexamic acid (TXA) and ε-aminocaproic acid (EACA).[106,130] Various studies have shown that TXA is effective at reducing blood loss, bleeding complications, and the need for reoperation without increasing mortality.[131-133] Higher dosing regimens, however, have been associated with an increase in postoperative seizures.[131,132,134] Data on EACA in cardiac surgery are more limited, but there do not appear to be meaningful differences compared with TXA.[106,135] In a study vs standard of care, EACA reduced postoperative RBC transfusion requirements in high-risk cardiac surgery and reduced the use of other blood components in all cohorts.[136]

rFVIIa has also been effective in reducing bleeding and blood component transfusion, even at very low doses.[137-139] However, the use of rFVIIa can be an independent predictor for the development of thromboembolic events.[114,138] Although much of this thrombotic risk was associated with the higher doses administered to patients with hemophilia, even at lower doses, rFVIIa should be used with caution. Use should be restricted to extreme circumstances, such as intractable nonsurgical bleeding unresponsive to standard hemostatic therapies, and rFVIIa should not be used to postpone reexploration.[106,114,138,140]

Another potential treatment option to reduce refractory bleeding that can be incorporated as part of a multifaceted coagulation management strategy is the use of PCCs postoperatively for patients exhibiting a documented coagulopathy.[106,114,141] Although comparative data are lacking, a 4-factor PCC may exhibit similar hemostatic efficacy to rFVIIa with a lower incidence of adverse events. One retrospective cohort study in patients undergoing cardiac surgery showed a significant reduction in cryoprecipitate transfusion, with no significant difference in inpatient mortality or blood component transfusion.[142]

In several small studies, a PCC was more effective at reducing transfusion than plasma without an increased thrombotic risk.[141,143-147] The reduced efficacy of plasma may be partially due to underdosing secondary to variable levels of clotting factors in donated plasma, and the risk of transfusion-associated lung injury with plasma must be considered.[146] Further confirmation of the safety profile of PCC is needed in multicenter randomized controlled trials,[141,146] although PCC use has been advocated for in Canada and some European countries.[148-150]

Because clot formation and strength rely heavily on fibrinogen levels,[151] preoperative fibrinogen concentration should be measured before cardiac surgery to guide hemostatic interventions, particularly in those at high risk of bleeding. Acquired hypofibrinogenemia after cardiac surgery frequently occurs due to hemodilution on CPB.[152] In this scenario, various studies have shown that administration of fibrinogen concentrate effectively reduces bleeding and decreases blood component transfusion requirements,[153-156] despite a lack of large-scale studies investigating safety. Data suggest noninferiority between fibrinogen concentrate and cryoprecipitate, and additional advantages of fibrinogen concentrate include shorter and simpler infusion times compared with cryoprecipitate.[157,158] Furthermore, fibrinogen concentrate has generally exhibited a favorable safety profile with a low risk of thromboembolic events.[151,158,159] Optimal dosing of fibrinogen

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remains undefined. Although 150 mg/dL is traditionally considered an adequate fibrinogen threshold for replacement, higher values may be necessary for hemostasis in patients having undergone CPB, especially in those who are severely coagulopathic.[160-163]

CONCLUSIONS

Excessive perioperative bleeding in cardiac surgery is associated with significant adverse outcomes. These consensus statements, developed by an international panel of experts, aim to reduce bleeding and work toward a more comprehensive quality metric to improve outcomes. Broad discussion is needed to establish a universal definition of excessive bleeding, standardized PBM strategies, and performance quality indicators beyond the reexploration rate, such as using bleeding checklists and time to reexploration, to more accurately measure the quality of care and improve patient outcomes.

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REFERENCES

1. Al-Attar N, Johnston S, Jamous N, et al. Impact of bleeding complications on length of stay and critical care utilization in cardiac surgery patients in England. *J Cardiothorac Surg*. 2019;14:64.

2. Al-Attar N, Gaer J, Giordano V, et al. Multidisciplinary paper on patient blood management in cardiothoracic surgery in the UK: perspectives on practice during COVID-19. *J Cardiothorac Surg*. 2023;18:96.

3. Konigstein M, Havakuk O, Arbel Y, et al. Impact of hemoglobin drop, bleeding events, and red blood cell transfusions on long-term mortality in patients undergoing transaortic valve implantation. *Can J Cardiol*. 2016;32:1239.e9-1239.e14.

4. Konigstein M, Ben-Assa E, Banai S, et al. Periprocedural bleeding, acute kidney injury, and long-term mortality after transcatheter aortic valve implantation. *Can J Cardiol*. 2015;31:56-62.

5. Karkouti K, Wijeysundera DN, Yau TM, et al. The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion*. 2004;44:1453-1462.

6. Pilgrim T, Stortecky S, Luterbacher F, Windecker S, Wenaweser P. Transcatheter aortic valve implantation and bleeding: incidence, predictors and prognosis. *J Thromb Thrombolysis*. 2013;35:456-462.

7. Newcomb AE, Dignan R, McElduff P, Pearse EJ, Bannon P. Bleeding after cardiac surgery is associated with an increase in the total cost of the hospital stay. *Ann Thorac Surg*. 2020;109:1069-1078.

8. Iannitti DA, Kim C, Ito D, Epstein J. Impact of an active hemostatic product treatment approach on bleeding-related complications and hospital costs among inpatient surgeries in the United States. *J Med Econ*. 2021;24:514-523.

9. Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. *J Thorac Cardiovasc Surg*. 2014;147:1458-1463.e1451.

10. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation*. 2011;123:2736-2747.

11. Colson PH, Gaudard P, Fellahi JL, et al. Active bleeding after cardiac surgery: a prospective observational multicenter study. *PLoS One*. 2016;11:e0162396.

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12. Ranucci M, Baryshnikova E, Castelvecchio S, Pelissero G. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. *Ann Thorac Surg*. 2013;96:478–485.

13. Mariscalco G, Gherli R, Ahmed AB, et al. Validation of the European multicenter study on coronary artery bypass grafting (E-CABG) bleeding severity definition. *Ann Thorac Surg*. 2016;101:1782–1788.

14. Xi Z, Gao Y, Yan Z, Zhou YJ, Liu W. The prognostic significance of different bleeding classifications in off-pump coronary artery bypass grafting. *BMC Cardiovasc Disord*. 2020;20:3.

15. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47:207–214.

16. Lewis KM, Li Q, Jones DS, et al. Development and validation of an intraoperative bleeding severity scale for use in clinical studies of hemostatic agents. *Surgery*. 2017;161:771–781.

17. Spotnitz WD, Zielske D, Centis V, et al. The SPOT GRADE: a new method for reproducibly quantifying surgical wound bleeding. *Spine (Phila Pa 1976)*. 2018;43:E664–E671.

18. Sciubba DM, Khanna N, Pennington Z, Singh RK. VIBe scale: validation of the intraoperative bleeding severity scale by spine surgeons. *Int J Spine Surg*. 2022;16:740–747.

19. Tan EK, Mayya R, Kruger D, Siriwardena AK, Goh BKP. Validation of VIBe bleeding scale amongst hepatopancreatobiliary surgeons: results from an IHPBA survey. *HPB (Oxford)*. 2023;25:1121–1125.

20. Siebert TM, Lewis KM, Shander A, O'Hanlan KA. Validated intraoperative bleeding scale (VIBe scale): relevance and utility in gynecological surgery. *J Minim Invasive Gynecol*. 2019;26(suppl):S52.

21. Ramirez M, Ramirez Almazán MA, Lewis K. PSU6 Economic impact of a validated intraoperative bleeding scale: a retrospective multicenter review from the US prospective. *Value Health*. 2019;22:S893.

22. Biancari F, Ruggieri VG, Perrotti A, et al. European multicenter study on coronary artery bypass grafting (E-CABG registry): study protocol for a prospective clinical registry and proposal of classification of postoperative complications. *J Cardiothorac Surg*. 2015;10:90.

23. Vranckx P, White HD, Huang Z, et al. Validation of BARC bleeding criteria in patients with acute coronary syndromes: the TRACER trial. *J Am Coll Cardiol*. 2016;67:2135–2144.

24. van Baarle F, van de Weerdt EK, Suurmond B, Müller MCA, Vlaar APJ, Biemond BJ. Bleeding assessment and bleeding severity in thrombocytopenic patients undergoing invasive procedures. *Transfusion*. 2020;60:637–649.

25. Gaizo DJD, Spotnitz WD, Hoffman RW, et al. SPOT GRADE II: clinical validation of a new method for reproducibly quantifying surgical wound bleeding: prospective, multicenter, multispecialty, single-arm study. *Clin Appl Thromb Hemost*. 2020;26:1076029620936340.

26. Karkouti K, O'Farrell R, Yau TM, Beattie WS. Prediction of massive blood transfusion in cardiac surgery. *Can J Anaesth*. 2006;53:781–794.

27. Magruder JT, Belmustakov S, Ohkuma R, et al. Attributable harm of severe bleeding after cardiac surgery in hemodynamically stable patients. *Gen Thorac Cardiovasc Surg*. 2017;65:102–109.

28. Ad N, Massimiano PS, Rongione AJ, et al. Number and type of blood products are negatively associated with outcomes after cardiac surgery. *Ann Thorac Surg*. 2022;113:748–756.

29. Marteinsson SA, Heimisdóttir AA, Axelsson TA, et al. Reoperation for bleeding following coronary artery bypass surgery with special focus on long-term outcomes. *Scand Cardiovasc J*. 2020;54:265–273.

30. Spadaccio C, Rose D, Nenna A, Taylor R, Bittar MN. Early re-exploration versus conservative management for postoperative bleeding in stable patients after coronary artery bypass grafting: a propensity matched study. *J Clin Med*. 2023;12:13.

31. Ohmes LB, Di Franco A, Guy TS, et al. Incidence, risk factors, and prognostic impact of re-exploration for bleeding after cardiac surgery: a retrospective cohort study. *Int J Surg*. 2017;48:166–173.

32. De Santo LS, Amarelli C, Della Corte A, et al. Blood transfusion after on-pump coronary artery bypass grafting: focus on modifiable risk factors. *Eur J Cardiothorac Surg*. 2013;43:359–366.

33. Hsu PS, Yang HY, Chen JL, et al. The implication of seniority of supervising attending surgeon on the reexploration rate following elective coronary artery bypass grafting. *J Formos Med Assoc*. 2019;118:354–361.

34. Shander A, Corwin HL, Meier J, et al. Recommendations from the International Consensus Conference on Anemia Management in surgical patients (ICCAMS). *Ann Surg*. 2023;277:581–590.

35. Isil CT, Yazici P, Bakir I. Risk factors and outcome of increased red blood cell transfusion in cardiac surgical patients aged 65 years and older. *Thorac Cardiovasc Surg*. 2015;63:39–44.

36. Liu Y, Wang X, Chen ZY, et al. Severe bleeding following off-pump coronary artery bypass grafting: Predictive factors and risk model. *J Geriatr Cardiol*. 2021;18:449–461.

37. O'Shaughnessy S, Tangel V, Dzotsi S, Jiang S, White R, Hoyler M. Non-white race/ethnicity and female sex are associated with increased allogeneic red blood cell transfusion in cardiac surgery patients: 2007–2018. *J Cardiothorac Vasc Anesth*. 2022;36:1908–1918.

38. Biancari F, Brascia D, Onorati F, et al. Prediction of severe bleeding after coronary surgery: the WILL-BLEED risk score. *Thromb Haemost*. 2017;117:445–456.

39. Gunertem E, Urcun S, Pala AA, Budak AB, Ercisli MA, Gunaydin S. Predictiveness of different preoperative risk assessments for postoperative bleeding after coronary artery bypass grafting surgery. *Perfusion-UK*. 2021;36:277–284.

40. Khan B, Islam MU, Ahmad I, Rehman MU. Modifiable risk factors associated with post-operative bleeding and transfusion requirements in cardiac surgery. *Pak J Med Sci*. 2022;38:855–861.

41. Gaba DM, Howard SK, Jump B. Production pressure in the work environment. California anesthesiologists' attitudes and experiences. *Anesthesiology*. 1994;81:488–500.

42. Everson MG, Wilbanks BA, Boust RR. Exploring production pressure and normalization of deviance and their relationship to poor patient outcomes. *AANA J*. 2020;88:365–371.

43. Wilbanks BA. Evaluation of methods to measure production pressure: a literature review. *J Nurs Care Qual*. 2020;35:E14–E19.

44. Carayon P. Production Pressures. May 1, 2007. Patient Safety Network. Accessed April 9, 2024. https://psnet.ahrq.gov/web-mm/production-pressures?_gl=1*e7ni0g*_ga*MjEzMTkxMTIzNy4xNjkyOTY5MDk4*_ga_45NDTD15CJ*MTY50DQxNDgzOC4xLjAuMTY50DQxNDgzOC42MC4wLjA

45. Kinnunen EM, De Feo M, Reichart D, et al. Incidence and prognostic impact of bleeding and transfusion after coronary surgery in low-risk patients. *Transfusion*. 2017;57:178–186.

46. ul Islam M, Ahmad I, Khan B, et al. Early chest re-exploration for excessive bleeding in post cardiac surgery patients: does it matter? *Cureus*. 2021;13:7.

47. Agarwal S, Choi SW, Fletcher SN, Klein AA, Gill R. The incidence and effect of resternotomy following cardiac surgery on morbidity and mortality: a 1-year national audit on behalf of the association of cardiothoracic anaesthesia and critical care. *Anaesthesia*. 2021;76:19–26.

48. Rodrigues ARB, Benevides LMB, Crespo JCL, Santana-Santos E, Püschel VAA, Oliveira LB. Factors associated with reoperation due to bleeding and outcomes after cardiac surgery: a prospective cohort study. *Rev Esc Enferm USP*. 2022;56(spe):e20210451.

49. Milojevic M, Bond C, He C, et al. Failure to rescue: Variation in mortality after cardiac surgery. *Interact Cardiovasc Thorac Surg*. 2021;33:848–856.

50. Qazi SM, Kandler K, Olsen PS. Reoperation for bleeding in an elective cardiac surgical population—does it affect survival? *J Cardiovasc Thorac Res*. 2021;13:198–202.

51. Čanádyová J, Zmeko D, Mokráček A. Re-exploration for bleeding or tamponade after cardiac operation. *Interact Cardiovasc Thorac Surg*. 2012;14:704–707.

52. Ruel M, Chan V, Boodhwani M, et al. How detrimental is reexploration for bleeding after cardiac surgery? *J Thorac Cardiovasc Surg*. 2017;154:927-935.

53. Shou BL, Aravind P, Ong CS, et al. Early reexploration for bleeding is associated with improved outcome in cardiac surgery. *Ann Thorac Surg*. 2023;115:232-239.

54. Agarwal S, Abdelmotieleb M. Viscoelastic testing in cardiac surgery. *Transfusion*. 2020;60(suppl 6):S52-S60.

55. Jeong D, Kim SY, Gu JY, Kim HK. Assessment of rotational thromboelastometry and thrombin generation assay to identify risk of high blood loss and re-operation after cardiac surgery. *Clin Appl Thromb Hemost*. 2022;28:7.

56. Raspé C, Besch M, Charitos EI, et al. Rotational thromboelastometry for assessing bleeding complications and factor XIII deficiency in cardiac surgery patients. *Clin Appl Thromb Hemost*. 2018;24(suppl):136s-144s.

57. Bartoszko J, Li H, Fitzgerald J, et al. The association of thrombin generation with bleeding outcomes in cardiac surgery: a prospective observational study. *Can J Anaesth*. 2022;69:311-322.

58. Vlot EA, van Dongen EPA, Willemsen LM, et al. Association of plasma fibrinogen and thromboelastography with blood loss in complex cardiac surgery. *Clin Appl Thromb Hemost*. 2021;27:10760296211016541.

59. Ranucci M, Baryshnikova E, Pistuddi V, Menicanti L, Frigiola A. The effectiveness of 10 years of interventions to control postoperative bleeding in adult cardiac surgery. *Interact Cardiovasc Thorac Surg*. 2017;24:196-202.

60. Ichikawa J, Marubuchi T, Nishiyama K, et al. Introduction of thromboelastometry-guided administration of fresh-frozen plasma is associated with decreased allogeneic blood transfusions and postoperative blood loss in cardiopulmonary-bypass surgery. *Blood Transfus*. 2018;16:244-252.

61. Karkouti K, Callum J, Wijeysundera DN, et al. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. *Circulation*. 2016;134:1152-1162.

62. Karkouti K, McCluskey SA, Callum J, et al. Evaluation of a novel transfusion algorithm employing point-of-care coagulation assays in cardiac surgery: a retrospective cohort study with interrupted time-series analysis. *Anesthesiology*. 2015;122:560-570.

63. Kuiper GJAJM, van Egmond LT, Henskens YMC, et al. Shifts of transfusion demand in cardiac surgery after implementation of rotational thromboelastometry-guided transfusion protocols: analysis of the HEROES-CS (HEmostasis Registry of patiEntS in Cardiac Surgery) observational, prospective open cohort database. *J Cardiothorac Vasc Anesth*. 2019;33:307-317.

64. Rodriguez-Martin I, Sanchez-Mora C, Fernandez-Lopez AR, et al. Evaluation of health outcomes after the implementation of rotational thromboelastometry in patients undergoing cardiac surgery. *Scand J Clin Lab Invest*. 2022;82:143-149.

65. Redfern RE, Fleming K, March RL, et al. Thrombelastography-directed transfusion in cardiac surgery: impact on postoperative outcomes. *Ann Thorac Surg*. 2019;107:1313-1318.

66. Kankaria A, Majumdar M, Lee S, et al. Platelet function testing and clinical outcomes in peripheral arterial disease: systematic review and narrative synthesis. *J Vasc Surg*. 2024;80(1):269-278.

67. Grove EL, Hossain R, Storey RF. Platelet function testing and prediction of procedural bleeding risk. *Thromb Haemost*. 2013;109:817-824.

68. Petricevic M, Konosic S, Biocina B, et al. Bleeding risk assessment in patients undergoing elective cardiac surgery using ROTEM(®) platelet and Multiplate(®) impedance aggregometry. *Anaesthesia*. 2016;71:636-647.

69. Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. *Vasc Health Risk Manag*. 2015;11:133-148.

70. Wells FC, Cooper DK, Milstein BB, English TA. Emergency open-heart surgery. Experience with 100 consecutive cases. *Scand J Thorac Cardiovasc Surg*. 1982;16:47-50.

71. Chilbert MR, Salah S, Kersten B, Nitsche L, Castoro N, El-Ashry A. Effect of P2Y12 platelet reactivity level on peri- and postoperative outcomes of cardiac surgery patients. *J Cardiovasc Surg (Torino)*. 2023;64:443-449.

72. Reed GW, Kumar A, Guo J, et al. Point-of-care platelet function testing predicts bleeding in patients exposed to clopidogrel undergoing coronary artery bypass grafting: verify pre-op TIMI 45—a pilot study. *Clin Cardiol*. 2015;38:92-98.

73. Rosengart TK, Romeiser JL, White LJ, et al. Platelet activity measured by a rapid turnaround assay identifies coronary artery bypass grafting patients at increased risk for bleeding and transfusion complications after clopidogrel administration. *J Thorac Cardiovasc Surg*. 2013;146:1259-1266, 1266.e1251 [discussion: 1266].

74. Gross L, Jochheim D, Nitschke T, et al. Platelet reactivity and early outcomes after transfemoral aortic valve implantation. *Thromb Haemost*. 2018;118:1832-1838.

75. Altheeb Z, Sbitan A, Shabiah M, et al. Platelet reactivity unit in predicting risk of bleeding in patients undergoing coronary artery bypass graft surgery. *Am J Ther*. 2016;23:e1537-e1541.

76. Kodaka M, Ichikawa J, Ando K, Komori M. Thromboelastometry and a hemostasis management system are most beneficial for guiding hemostatic therapy in cardiac surgery patients with a EuroSCORE II of ≥1.83%: a randomized controlled two-step trial. *J Anesth*. 2020;34:666-674.

77. Kallioinen M, Valtonen M, Peltoniemi M, et al. Effects of implementing rotational thromboelastometry in cardiac surgery: a retrospective cohort study. *J Perioper Pract*. 2021;31:326-333.

78. Bolcato M, Russo M, Trentino K, Isbister J, Rodriguez D, Aprile A. Patient blood management: the best approach to transfusion medicine risk management. *Transfus Apher Sci*. 2020;59:102779.

79. Ozawa S, Ozawa-Morriello J, Rock R, et al. Patient blood management as an emerging concept in quality: the role of nurses. *J Nurs Care Qual*. 2024;39:129-135.

80. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med*. 2017;377:2133-2144.

81. Carson JL, Brooks MM, Hébert PC, Goodman SG, et al. Restrictive or liberal transfusion strategy in myocardial infarction and anemia. *N Engl J Med*. 2023;389:2446-2456.

82. Carson JL, Stanworth SJ, Guyatt G, et al. Red blood cell transfusion: 2023 AABB international guidelines. *JAMA*. 2023;330:1892-1902.

83. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the reality randomized clinical trial. *JAMA*. 2021;325:552-560.

84. Irving AH, Harris A, Petrie D, Higgins A, Smith J, McQuilten ZK. Impact of patient blood management guidelines on blood transfusions and patient outcomes during cardiac surgery. *J Thorac Cardiovasc Surg*. 2020;160:437-445.e420.

85. Yaffee DW, Smith DE 3rd, Ursomanno PA, et al. Management of blood transfusion in aortic valve surgery: impact of a blood conservation strategy. *Ann Thorac Surg*. 2014;97:95-101.

86. Ternström L, Hyllner M, Backlund E, Schersten H, Jeppsson A. A structured blood conservation programme reduces transfusions and costs in cardiac surgery. *Interact Cardiovasc Thorac Surg*. 2014;19:788-794.

87. Scolletta S, Simioni P, Campagnolo V, et al. Patient blood management in cardiac surgery: the "Granducato algorithm." *Int J Cardiol*. 2019;289:37-42.

88. Gross I, Seifert B, Hofmann A, Spahn DR. Patient blood management in cardiac surgery results in fewer transfusions and better outcome. *Transfusion*. 2015;55:1075-1081.

89. Pearse BL, Smith I, Faulke D, et al. Protocol guided bleeding management improves cardiac surgery patient outcomes. *Vox Sang*. 2015;109:267-279.

ARTICLE IN PRESS

90. Pearse BL, Keogh S, Rickard CM, et al. Bleeding management practices of Australian cardiac surgeons, anesthesiologists and perfusionists: a cross-sectional national survey incorporating the theoretical domains framework (TDF) and COM-B model. *J Multidiscip Healthc*. 2020;13:27-41.

91. Cote C, MacLeod JB, Yip AM, et al. Variation in transfusion rates within a single institution: Exploring the effect of differing practice patterns on the likelihood of blood product transfusion in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg*. 2015;149:297-302.

92. Vonk AB, Meesters MI, Garnier RP, et al. Intraoperative cell salvage is associated with reduced postoperative blood loss and transfusion requirements in cardiac surgery: a cohort study. *Transfusion*. 2013;53:2782-2789.

93. Neef V, Vo L, Herrmann E, et al. The association between intraoperative cell salvage and red blood cell transfusion in cardiac surgery an observational study in a patient blood management centre. *Anaesthesiol Intensive Ther*. 2021;53:1-9.

94. Zhao H, Ma H, Meng L, Zhao Z, Quan X, Cheng Z. Application of autologous blood cell salvage in off-pump coronary artery bypass graft operation. *Heart Surg Forum*. 2017;20:E107-E110.

95. Shen S, Zhang J, Wang W, Zheng J, Xie Y. Impact of intra-operative cell salvage on blood coagulation in high-bleeding-risk patients undergoing cardiac surgery with cardiopulmonary bypass: a prospective randomized and controlled trial. *J Transl Med*. 2016;14:228.

96. Xie Y, Shen S, Zhang J, Wang W, Zheng J. The efficacy, safety and cost-effectiveness of intra-operative cell salvage in high-bleeding-risk cardiac surgery with cardiopulmonary bypass: a prospective randomized and controlled trial. *Int J Med Sci*. 2015;12:322-328.

97. Adam EH, Funke M, Zacharowski K, Meybohm P, Keller H, Weber CF. Impact of intraoperative cell salvage on blood coagulation factor concentrations in patients undergoing cardiac surgery. *Anesth Analg*. 2020;130:1389-1395.

98. Zimmermann E, Zhu R, Ogami T, et al. Intraoperative autologous blood donation leads to fewer transfusions in cardiac surgery. *Ann Thorac Surg*. 2019;108:1738-1744.

99. Henderson RA, Mazzeffi MA, Strauss ER, et al. Impact of intraoperative high-volume autologous blood collection on allogeneic transfusion during and after cardiac surgery: a propensity score matched analysis. *Transfusion*. 2019;59:2023-2029.

100. Barile L, Fominskiy E, Di Tomasso N, et al. Acute normovolemic hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis of randomized trials. *Anesth Analg*. 2017;124:743-752.

101. Li S, Liu Y, Zhu Y. Effect of acute normovolemic hemodilution on coronary artery bypass grafting: a systematic review and meta-analysis of 22 randomized trials. *Int J Surg*. 2020;83:131-139.

102. Murray D. Acute normovolemic hemodilution. *Eur Spine J*. 2004;13(suppl 1):S72-S75.

103. Naqash IA, Draboo MA, Lone AQ, Nengroo SH, Kirmani A, Bhat AR. Evaluation of acute normovolemic hemodilution and autotransfusion in neurosurgical patients undergoing excision of intracranial meningioma. *J Anaesthesiol Clin Pharmacol*. 2011;27:54-58.

104. Hofmann B, Kaufmann C, Stiller M, et al. Positive impact of retrograde autologous priming in adult patients undergoing cardiac surgery: a randomized clinical trial. *J Cardiothorac Surg*. 2018;13:50.

105. Saczkowski R, Bernier P-L, Tchervenkov CI, Arellano R. Retrograde autologous priming and allogeneic blood transfusions: a meta-analysis. *Interact Cardiovasc Thorac Surg*. 2009;8:373-376.

106. Tibi P, McClure RS, Huang J, et al. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. *J Extra Corpor Technol*. 2021;53:97-124.

107. Hensley NB, Cho BC, Visagie M, Lester LC, Abernathy JH 3rd, Frank SM. How do I audit intraoperative blood component utilization in cardiac surgery? *Transfusion*. 2019;59:3058-3064.

108. Raphael J, Mazer CD, Subramani S, et al. Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory for Management of Perioperative Bleeding and Hemostasis in Cardiac Surgery Patients. *Anesth Analg*. 2019;129:1209-1221.

109. Loor G, Vivacqua A, Sabik JF, et al. Process improvement in cardiac surgery: development and implementation of a reoperation for bleeding checklist. *J Thorac Cardiovasc Surg*. 2013;146:1028-1032.

110. Pearse BL, Rickard CM, Keogh S, Fung YL. A retrospective explanatory case study of the implementation of a bleeding management quality initiative, in an Australian cardiac surgery unit. *Aust Crit Care*. 2019;32:92-99.

111. The Society of Thoracic Surgeons. STS National Database. Accessed April 9, 2024. https://www.sts.org/sts-national-database#:~:text=The%20STS%20Adult%20Cardiac%20Surgery,physicians%2C%20including%20surgeons%20and%20anesthesiologists

112. Elassal AA, Al-Ebrahim KE, Debis RS, et al. Re-exploration for bleeding after cardiac surgery: revaluation of urgency and factors promoting low rate. *J Cardiothorac Surg*. 2021;16:166.

113. van Boxtel AGM, van Veghel D, Soliman Hamad MA, Schulz DN, Stepaniak PS, van Straten AHM. Use of an intraoperative checklist to decrease the incidence of re-exploration for postoperative bleeding after cardiac surgery. *Interact Cardiovasc Thorac Surg*. 2017;25:555-558.

114. Pagano D, Milojevic M, Meesters MI, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *Eur J Cardiothorac Surg*. 2018;53:79-111.

115. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med*. 2019;179:1469-1478.

116. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. *Am J Hematol*. 2019;94:697-709.

117. Heuts S, Ceulemans A, Kuiper G, et al. Optimal management of cardiac surgery patients using direct oral anticoagulants: recommendations for clinical practice. *Eur J Cardiothorac Surg*. 2023;64:ezad340.

118. Spyropoulos AC, Hartaigh B, Cao Z, et al. Costs and healthcare resource utilization associated with idarucizumab or andexanet alfa oral anticoagulant reversal in patients hospitalized with life-threatening bleeds. *Clin Appl Thromb Hemost*. 2022;28:10760296221110568.

119. Dohle D-S, Pfeiffer P, Probst C, Treede H. Andexanet alfa and heparin resistance in cardiac surgery: Experiences and risks associated with the reversal of direct oral anticoagulants. *Eur J Cardiothorac Surg*. 2023;63:ezad189.

120. Abdulrehman J, Zarabi S, Elbaz C, et al. Safety of idarucizumab in the reversal of dabigatran at six tertiary care Ontario hospitals. *Res Pract Thromb Haemost*. 2021;5:e12535.

121. Erdoes G, Martinez Lopez De Arroyabe B, Bolliger D, et al. International consensus statement on the peri-operative management of direct oral anticoagulants in cardiac surgery. *Anaesthesia*. 2018;73:1535-1545.

122. Hassan K, Thielmann M, Easo J, et al. Removal of apixaban during emergency cardiac surgery using hemoadsorption with a porous polymer bead sorbent. *J Clin Med*. 2022;11:5889.

123. Matejic-Spasic M, Hassan K, Thielmann M, et al. Management of perioperative bleeding risk in patients on antithrombotic medications undergoing cardiac surgery—a systematic review. *J Thorac Dis*. 2022;14:3030-3044.

124. Jackson R, Trus RM, El-Diasty M. Hemadsorption for removal of ticagrelor and direct oral anticoagulants in cardiac surgery. *Expert Rev Cardiovasc Ther*. 2022;20:141-150.

125. Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. *Br J Anaesth*. 2015;115:376-385.

126. Chello M, Nenna A. Continuing aspirin before coronary artery bypass grafting surgery: old fears challenged by new evidences. *Ann Transl Med*. 2016;4(suppl 1):S34.

127. Nenna A, Spadaccio C, Prestipino F, et al. Effect of preoperative aspirin replacement with enoxaparin in patients undergoing primary isolated on-pump coronary artery bypass grafting. *Am J Cardiol*. 2016;117:563-570.

128. Myles PS, Smith JA, Forbes A, et al. Stopping vs. continuing aspirin before coronary artery surgery. *N Engl J Med*. 2016;374:728-737.

ARTICLE IN PRESS

129. Engelman DT, Ben Ali W, Williams JB, et al. Guidelines for perioperative care in cardiac surgery: Enhanced Recovery After Surgery Society recommendations. *JAMA Surg*. 2019;154:755-766.

130. Klein A, Agarwal S, Cholley B, et al. A review of European guidelines for patient blood management with a particular emphasis on antifibrinolytic drug administration for cardiac surgery. *J Clin Anesth*. 2022;78:110654.

131. Maeda T, Ishihara T, Miyata S, et al. Evaluating the effect on mortality of a no-tranexamic acid (TXA) policy for cardiovascular surgery. *J Cardiothorac Vasc Anesth*. 2018;32:1627-1634.

132. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med*. 2017;376:136-148.

133. Zhang Y, Gao X, Yuan S, et al. Effects of tranexamic acid on short-term and long-term outcomes of on-pump coronary artery bypass grafting: randomized trial and 7-year follow-up. *Cardiovasc Ther*. 2018;36:e12472.

134. Shi J, Zhou C, Pan W, et al. Effect of high-vs low-dose tranexamic acid infusion on need for red blood cell transfusion and adverse events in patients undergoing cardiac surgery: the optimal randomized clinical trial. *JAMA*. 2022;328:336-347.

135. Leff J, Rhee A, Nair S, Lazar D, Sathyanarayana SK, Shore-Lesserson L. A randomized, double-blinded trial comparing the effectiveness of tranexamic acid and epsilon-aminocaproic acid in reducing bleeding and transfusion in cardiac surgery. *Ann Card Anaesth*. 2019;22:265-272.

136. Kelava M, Mehta A, Sale S, et al. Effectiveness and safety of E-aminocaproic acid in overall and less-invasive cardiac surgeries. *J Cardiothorac Vasc Anesth*. 2022;36:3780-3790.

137. Cotter E, Sharma A, Campton A, et al. Very low-dose recombinant factor VIIa administration for cardiac surgical bleeding reduces red blood cell transfusions and renal risk: a matched cohort study. *Blood Coagul Fibrinolysis*. 2021;32:473-479.

138. Habib AM, Calafiore AM, Cargoni M, Foschi M, Di Mauro M. Recombinant activated factor VII is associated with postoperative thromboembolic adverse events in bleeding after coronary surgery. *Interact Cardiovasc Thorac Surg*. 2018;27:350-356.

139. Hoffmann T, Assmann A, Dierksen A, et al. A role for very low-dose recombinant activated factor VII in refractory bleeding after cardiac surgery: lessons from an observational study. *J Thorac Cardiovasc Surg*. 2018;156:1564-1573.e1568.

140. Tomita E, Takase H, Tajima K, Suematsu Y. Change of coagulation after NovoSeven® use for bleeding during cardiac surgery. *Asian Cardiovasc Thorac Ann*. 2017;25:99-104.

141. Fitzgerald J, Lenihan M, Callum J, et al. Use of prothrombin complex concentrate for management of coagulopathy after cardiac surgery: a propensity score matched comparison to plasma. *Br J Anaesth*. 2018;120:928-934.

142. Hyland SJ, James DC, Gordon EM, et al. Prothrombin complex concentrate vs factor VII for refractory bleeding in cardiac surgery. *Ann of Thorac Surg Short Rep*. 2023;1:691-695.

143. Biancari F, Ruggieri VG, Perrotti A, et al. Comparative analysis of prothrombin complex concentrate and fresh frozen plasma in coronary surgery. *Heart Lung Circ*. 2019;28:1881-1887.

144. Karkouti K, Bartoszko J, Grewal D, et al. Comparison of 4-factor prothrombin complex concentrate with frozen plasma for management of hemorrhage during and after cardiac surgery: a randomized pilot trial. *JAMA Netw Open*. 2021;4:e213936.

145. Bartoszko J, Callum J, Karkouti K. The association of prothrombin complex concentrates with postoperative outcomes in cardiac surgery: an observational substudy of the FIBRES randomized controlled trial. *Can J Anesth*. 2021;68:1789-1801.

146. Roman M, Biancari F, Ahmed AB, et al. Prothrombin complex concentrate in cardiac surgery: a systematic review and meta-analysis. *Ann Thorac Surg*. 2019;107:1275-1283.

147. Smith MM, Schroeder DR, Nelson JA, et al. Prothrombin Complex Concentrate vs Plasma for Post-Cardiopulmonary Bypass Coagulopathy and Bleeding: a randomized clinical trial. *JAMA Surg*. 2022;157:757-764.

148. Canadian National Advisory Committee on Blood and Blood Products. Guidelines & Recommendations: Recommendations for Use of Prothrombin Complex Concentrates in Canada. Canadian National Advisory Committee on Blood and Blood Products. April 7, 2022. Accessed April 9, 2024. https://nacblood.Ca/en/resource/recommendations-use-prothrombin-complex-concentrates-canada

149. Erdoes G, Koster A, Ortmann E, et al. A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. *Anaesthesia*. 2021;76:381-392.

150. Boer C, Meesters MI, Milojevic M, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth*. 2018;32:88-120.

151. Hensley NB, Mazzeffi MA. Pro-con debate: fibrinogen concentrate or cryoprecipitate for treatment of acquired hypofibrinogenemia in cardiac surgical patients. *Anesth Analg*. 2021;133:19-28.

152. Besser MW, MacDonald SG. Acquired hypofibrinogenemia: current perspectives. *J Blood Med*. 2016;7:217-225.

153. Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. *Anesthesiology*. 2013;118:40-50.

154. Karlsson M, Ternström L, Hyllner M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost*. 2009;102:137-144.

155. Solomon C, Rahe-Meyer N. Fibrinogen concentrate as first-line therapy in aortic surgery reduces transfusion requirements in patients with platelet counts over or under 100×10^9/L. *Blood Transfus*. 2015;13:248-254.

156. Cushing MM, Haas T. Fibrinogen concentrate for perioperative bleeding: what can we learn from the clinical trials? *Transfusion*. 2019;59:3295-3297.

157. Ayaganov D, Kuanyshbek A, Vakhrushev I, Li T. Prospective, randomized study of fibrinogen concentrate versus cryoprecipitate for correcting hypofibrinogenemia in cardiac surgery patients. *J Cardiothorac Vasc Anesth*. 2024;38:80-85.

158. Callum J, Farkouh ME, Scales DC, et al. Effect of fibrinogen concentrate vs cryoprecipitate on blood component transfusion after cardiac surgery: the FIBRES randomized clinical trial. *JAMA*. 2019;322:1966-1976.

159. Solomon C, Gröner A, Ye J, Pendrak I. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. *Thromb Haemost*. 2015;113:759-771.

160. Waldén K, Jeppsson A, Nasic S, Backlund E, Karlsson M. Low preoperative fibrinogen plasma concentration is associated with excessive bleeding after cardiac operations. *Ann Thorac Surg*. 2014;97:1199-1206.

161. Karkouti K, Callum J, Crowther MA, et al. The relationship between fibrinogen levels after cardiopulmonary bypass and large volume red cell transfusion in cardiac surgery: an observational study. *Anesth Analg*. 2013;117:14-22.

162. Ranucci M, Pistuddi V, Baryshnikova E, Colella D, Bianchi P. Fibrinogen levels after cardiac surgical procedures: association with postoperative bleeding, trigger values, and target values. *Ann Thorac Surg*. 2016;102:78-85.

163. Kindo M, Hoang Minh T, Gerelli S, et al. Plasma fibrinogen level on admission to the intensive care unit is a powerful predictor of postoperative bleeding after cardiac surgery with cardiopulmonary bypass. *Thromb Res*. 2014;134:360-368.